Neural Print Tuning and Audiovisual Integration Deficits in Dyslexic Adolescents

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“Ja, das grenzenloseste aller Abenteuer der Kindheit, das war das Leseabenteuer. Für mich begann es, als ich zum ersten Mal ein eigenes Buch bekam und mich da hineinschnupperte. In diesem Augenblick erwachte mein Lesehunger, und ein besseres Geschenk hat das Leben mir nicht beschert.”

Astrid Lindgren

“I took a speed-reading course and read War and Peace in twenty minutes. It involves Russia.”

Woody Allen

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Abstract

Current models on the aetiology of dyslexia advocate a core deficit in phonological processing that obstructs visual tuning of occipitotemporal brain regions to print. Such tuning is essential for the acquisition of efficient reading skills and reading speed is correlated with left occipitotemporal print tuning. The present thesis aims at clarifying two critical aspects of previous research.

The first study intends to provide unequivocal evidence for a lack of left ventral occipitotemporal tuning to print in dyslexic adolescents that were at the end of compulsory schooling. This is a critical developmental stage, given that reading proficiency is still trained at a high level before literacy experiences diverge due to different professional tracks. Previous studies have repeatedly shown underactivation in dyslexia within this brain region, but results might be confounded by interfering or mediating phonological processes, considering that this region is thought to be involved in relaying phonological (top-down) and visual (bottom-up) processes.

By means of a task that probes orthographic processing in a highly bottom-up manner, interfering phonological and other higher-order processes were minimized. In such a context, underactivation would provide important evidence that efficient visual print tuning has failed in dyslexic adolescents and that deficient tuning might be the proximate marker of impaired reading in the matured brain.

The second study aimed at narrowing down the nature of phonological deficits and in relating them to orthographic decoding. Increasing evidence points to impairments in grapho-phonological conversion, and such impairments have recently been put into a framework of aberrant audiovisual processing and integration in dyslexia. The study used two approaches to testing audiovisual integration, one focusing on the level of phonetic content (grapho-phonological conversion) and one focusing on more basic and sensory aspects of audiovisual integration. It provides the first comprehensive comparison of several approaches to testing audiovisual integration in dyslexia and on testing the generalizability of deficits in audiovisual processing.

Thirteen dyslexic adolescents and twenty-two matched typical readers participated in simultaneous electroencephalographic and functional magnetic resonance imaging measurements. This combination of techniques facilitates the investigation of neural processes and aberrances at both high temporal and high spatial resolution.

The results of Study 1 strikingly confirmed a lack of left ventral occipitotemporal print tuning in the dyslexic sample and provided unprecedentedly clear evidence that such impairments might be the long-term consequence of impaired phonological awareness since childhood.
Study 2 suggested specific impairments in superior temporal brain regions at the phonetic level (grapho-phonological conversion) rather than at more basic and sensory levels of audio-visual integration. Importantly, deficits in grapho-phonological conversion were especially apparent in a context of speech- and word-like stimulation that exhibited rapid acoustic changes. This points to most pronounced impairments when dealing with naturalistic stimulus material and argues against a basal deficit in audiovisual integration.
Taken together, both studies are in line with the hypothesis of phonologically guided left occipitotemporal tuning to print and a failure of such guidance and tuning in dyslexia. Impaired guidance by superior temporal brain regions relates to the earliest marker of DD, namely troublesome phonological awareness and processing. The lack of print tuning in ventral brain regions is the succeeding and persistent proximate marker of impaired reading, as demonstrated by correlations between hemodynamic signals and measures of reading fluency. It is therefore advisable to encourage phonological and especially grapho-phonological training programs in children at risk.

Zusammenfassung

Gegenwärtige Modelle zur Ätiologie von spezifischer Leseschwäche (Dyslexie) befürworten ein Kerndefizit in phonologischer Verarbeitung, das zur Beeinträchtigung von neuronaler Schriftspezialisierung in okzipitotemporalen Gehirnregionen führt. Schriftspezialisierung ist essenziell für den Erwerb effizienten Lesens und die Lesegeschwindigkeit korreliert mit links okzipitotemporaler Schriftspezialisierung. Die vorliegende Arbeit hat die Klärung zweier kritischer Aspekte bisheriger Forschungsbemühungen zum Ziel.

Studie 1 dient dem eindeutigen Beleg, dass links ventral-okzipitotemporale Schriftspezialisierung bei dyslektischen Jugendlichen gegen Ende der obligatorischen Schulzeit fehlt. Diese Entwicklungsstufe ist kritisch, da Lesefertigkeiten noch auf hohem Niveau trainiert werden bevor das Leseverhalten aufgrund unterschiedlicher Werdegänge auseinanderdriftet. Frühere Studien haben wiederholt Minderaktivität in dieser Gehirnregion bei Dyslexie gezeigt. Diese Befunde könnten jedoch durch überlagernde oder vermittelnde phonologische Prozesse konfundiert sein angesichts der Tatsache, dass dieser Region eine Verschaltungsfunktion von phonologischen (top-down) und visuellen (bottom-up) Prozessen zugesprochen wird.

Anhand eines Paradigmas, das orthographische Verarbeitung auf eine hochgradig visuell-sensorische Weise (bottom-up) prüft, wurden interferierende phonologische und andere Prozesse höherer Verarbeitungsstufen minimiert. In solch einem Kontext sollte Minderaktivierung ein nachhaltiger Beleg sein, dass effiziente Schriftspezialisierung bei dyslektischen Jugendlichen nicht vorhanden ist und dass mangelhafte Spezialisierung im gereiften Gehirn unmittelbar mit Leseschwäche zusammenhängt.

Studie 2 hatte zum Ziel, die genaue Beschaffenheit des phonologischen Defizits einzugrenzen und es in Beziehung zu orthographischer Verarbeitung zu setzen. Es mehren sich die Befunde zu Beeinträchtigungen in grapho-phonologischer Umwandlung und solch eine Beeinträchtigung wurde unlängst mit atypischer audiovisueller Verarbeitung und Integration bei Dyslexie in Verbindung gebracht. Die Studie wählte zwei Ansätze zur Testung audiovisueller Integration. Beim ersten Ansatz war die Ebene phonetischen Inhalts (grapho-phonologische Umwandlung) zentral, beim zweiten standen basalere und sensorische Aspekte audiovisueller Integration im Mittelpunkt. Die Studie stellt die erste umfassende Gegenüberstellung mehrerer Ansätze zur Testung audiovisueller Integration bei Dyslexie dar, sowie zur Prüfung der Generalisierbarkeit audiovisueller Verarbeitungsdefizite.

Dreizehn dyslektische Jugendliche und zweiundzwanzig gematchte typische Leser nahmen an simultanen elektroenzephalographischen und funktionellen Magnetresonanz Messungen teil. Diese Kombination von Methoden ermöglicht die Untersuchung neuronaler Prozesse und Atypikalitäten bei zugleich hoher zeitlicher und räumlicher Auflösung.

Die Ergebnisse der Studie 1 bestätigten nachdrücklich das Fehlen von links ventral-okzipitotemporaler Schriftspezialisierung in der Dyslexiegruppe und zeigten auf außerordentlich deutliche Weise, dass diese Defizite die Spätfolge von beeinträchtigter phonologischer Wahrnehmung seit der Kindheit sein könnten.

Studie 2 deutete auf spezifische Beeinträchtigungen in superior-temporalen Gehirnregionen hin, die sich insbesondere auf phonetischer Ebene (grapho-phonologische Umwandlung) auswirken und weniger auf einer basaleren und sensorischen Ebene der audiovisuellen Integration. Zudem zeigten sich die Defizite in grapho-phonologischer Umwandlung insbesondere im Kontext sprach- und wortähnlicher Stimulation von hoher akustischer Veränderlichkeit. Dies legt nahe, dass die stärkste Beeinträchtigung im Umgang mit realistischem Stimulusmaterial auftritt und weniger auf basale Defizite in audiovisueller Integration zurückzuführen ist.

Zusammengefasst gehen beide Studien konform mit der Hypothese phonologisch gesteuerter links okzipitotemporaler Schriftspezialisierung und einer entsprechenden Fehlsteuerung und -spezialisierung bei Dyslexie. Mangelhafte Steuerung durch superior-temporale Gehirnregionen steht in Bezug zum frühesten Vorboten von Dyslexie, nämlich beeinträchtigter phonologischer Wahrnehmung und Verarbeitung. Fehlende Schriftspezialisierung in ventralen Gehirnregionen ist der resultierende und beständige unmittelbare Marker beeinträchtigten Lesens, wie sich in Korrelationen zwischen hämodynamischem Signal und Leseflüssigkeitsmaßen zeigte. Es empfiehlt sich daher die frühe Förderung phonologischer und insbesondere grapho-phonologischer Trainingsprogramme bei Risikokindern.

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AV	audiovisual
BOLD	blood-oxygen-level dependent
CVC	consonant-vowel-consonant (string)
CVCa	unimodal auditory CVC
CVCv	unimodal visual CVC
CVCcon	congruent CVC
CVCinc	incongruent CVC
DD	developmental dyslexia
EEG	electroencephalography
ERP	event-related potential
FB	frequent bigram condition
FF	false font condition
fMRI	functional magnetic resonance imaging
GFP	global field power
IPL	inferior parietal lobule
M	mean
MTGp	posterior middle temporal gyrus
PT	planum temporale
RB	rare bigram condition
ROI	region of interest
SD	standard deviation
SEM	standard error of the mean
SLcon	congruent single letter stimuli
SLinc	incongruent single letter stimuli
SOA	stimulus onset asynchrony
STG	superior temporal gyrus
STGp	posterior superior temporal gyrus
STS	superior temporal sulcus
TANOVA	topographic analysis of variance
vOT	ventral occipitotemporal
W	word condition

1 Developmental Dyslexia

Reading is an essential competence in everyday life and for human communication, especially in our digital society with the advent of emails, Internet, Twitter, and so forth. Those who leisurely read each day are happier (Robinson & Martin, 2008) and live longer (Jacobs, Hammerman-Rozenberg, Cohen, & Stessman, 2008). Reading, however, is not an innate skill but the result of extensive explicit training. Acquired with relative ease by most pupils, a few among them will struggle with unexpected difficulties during learning to read. Such difficulties are termed dyslexia if certain conditions are met. Dyslexia is of Greek origin, translating roughly to abnormal (*dys*) word (*lex*) disease / condition (-*ia*).

1.1 Definition and Epidemiology

Developmental Dyslexia (DD) is a learning disability of neurobiological origin, characterized by specific impairments in the acquisition of efficient reading skills. Specific, because children and adults affected possess the intelligence and motivation considered necessary for successful reading. They also do not lack instruction or sociocultural opportunity (Lyon, Shaywitz, & Shaywitz, 2003; WHO, 1992)[1]. Exclusion criteria are acquired brain trauma or disease and impaired visual or auditory sensory acuity. Historically, the condition of "Wortblindheit" (word-blindness) was first described 135 years ago by Kussmaul (1877) as the inability to read words, despite being able to see them.

Nowadays, DD is perhaps the most common neurobehavioral disorder with a prevalence estimated between 5% and 17.5% in school-age children (S. E. Shaywitz, 1996). This wide range is a result of loose diagnostic criteria (e.g., with respect to the relation of IQ and reading scores (Stanovich, 1991)) and of cultural differences. For instance, a study of 5,718 children in a population-based birth cohort in the US reported a prevalence range of 5.3 to 11.8% (Katusic, Colligan, Barbaresi, Schaid, & Jacobsen, 2001), whereas prevalence rates are reportedly lower in Italy (Lindgren, De Renzi, & Richman, 1985) or Egypt (Farrag, el-Behary, & Kandil, 1988). Despite robust findings that diagnostic criteria are often overcome in adolescence and adulthood (Badian, 1999; Smart, Prior, Sanson, & Oberklaid, 2001; Wheldall & Limbrick, 2010; S. F. Wright, Fields, & Newman, 1996), DD is a persistent, chronic condi-

[1] The term dyslexia has recently been eliminated from the Diagnostic and Statistical Manual of Mental Disorders (DSM-V; APA, 2013). Learning Disorder has changed to Specific Learning Disorder and the sub-category Dyslexia is no longer recommended. The type of learning disorder will instead be specified during diagnosis. Withdrawal of these changes has been recommended (e.g., Colker, Shaywitz, Shaywitz, & Simon, 2013; Snowling & Hulme, 2012).

tion. Longitudinal studies have reported that poor readers and good readers tend to maintain their relative positions along a reading score continuum (Jacobson, 1999; B. A. Shaywitz, Holford, Holahan, Fletcher, & et al., 1995; Svensson & Jacobson, 2006). Retrospective studies also support persisting difficulties across the life span (Bruck, 1990; Felton, Naylor, & Wood, 1990).

A preponderance of studies claims that more boys than girls are reading impaired. Estimates of gender ratio (male:female) fluctuate around 2:1 to 3:1 (Badian, 1999; Chan, Ho, Tsang, Lee, & Chung, 2007; Coutinho & Oswald, 2005; Flannery, Liederman, Daly, & Schultz, 2000; Katusic et al., 2001; Miles, Haslum, & Wheeler, 1998; Olson, 2002; Rutter et al., 2004; Stevenson, 1992; Wheldall & Limbrick, 2010). Likewise, the Program for International Student Assessment (PISA) revealed consistently higher reading achievement in 15-year old girls compared to boys (Lynn & Mikk, 2009; see also Chiu & McBride-Chang, 2006). Specifically, boys seem to exhibit greater variance in reading levels with considerable clustering also at the lower end of the continuum, whereas the top end is predominated by girls (Machin & Pekkarinen, 2008). Gender differences may partially be explained by genetic factors, given that DD has a high hereditary risk. It is known for a long time that DD runs in families (e.g., Hinshelwood, 1907; Stephenson, 1907). Children who have a parent with dyslexia indicated to have the disorder themselves with a probability ranging from 34% (Rutter & Yule, 1975) to as much as 65% (Scarborough, 1990). Moreover, 20% to 33% of siblings of affected individuals, with unaffected parents, were affected themselves. If additionally one parent or both parents had DD, numbers increased to 54 – 63% or 76 – 78%, respectively (Gilger, Hanebuth, Smith, & Pennington, 1996). Family studies are good for first explorations of genetic influences on a disorder. However, they neglect that there is a high overlap in environmental factors within families that may also account for increases in familial clustering. Methodologically more sound results come from twin studies that compare concordance rates of monozygotic and dizygotic twins. Heritability, that is the proportion of phenotypic variation attributable to genetic variation, ranges from 30% to 70% (Castles, Datta, Gayan, & Olson, 1999; DeFries, Fulker, & LaBuda, 1987; Gayan & Olson, 2001; Stevenson, Graham, Fredman, & McLoughlin, 1987; Wadsworth, Olson, Pennington, & DeFries, 2000). Taken together, the heritability of DD is without doubt.

1.2 Diagnosis and Significance

As noted in the previous section, diagnostic criteria for dyslexia are loose. Naturally, tests of reading accuracy and / or fluency are mandatory for diagnosis. This means that formal diag-

nosis is impossible prior to formal reading instruction. Early indicators for toddlers at risk, especially from families affected, may be observed in the phonological domain. This includes late speaking, mispronunciations, difficulties with word retrieval, and confusing words that sound alike (S. E. Shaywitz, Morris, & Shaywitz, 2008). More formally, phonological deficits can be split into three subcomponents as shown in Table 1.1, namely phonological awareness, rapid automatized naming, and phonological working memory.

Table 1.1 Subdomains of phonological processes that are subject to deficits at the behavioural level

Subdomain	Description	Example
Phonological awareness	Awareness and manipulation of the sound structure of language	Rhyming, phoneme deletion
Phonological retrieval / rapid automatized naming	Speed of phonological access, which is necessary for articulation	Rapid object (later: digit / letter) naming
Phonological working memory	Short-term storage and retrieval of auditory input	Recall of auditory input, e.g. digit span, Mottier test

For each subdomain specific tests exist, too numerous to describe in detail within the scope of this thesis. With the beginning of formal reading instruction further indicators maybe observed, such as misreadings (especially unfamiliar words and small function words) and slow reading. Difficulties in spelling are also very common and they have been incorporated into ICD-10 (code F81.0; WHO, 1992) and DSM-IV (out-dated; APA, 2000) definitions of dyslexia. If indicators are obvious, special help should start as soon as possible. Interventions that are provided in the very first few years of school appear to be much more effective than at a later point (Torgesen et al., 2006). Moreover, interventions that target phonological deficits have repeatedly been shown effective in the amelioration of decoding and word-reading weaknesses in DD (Bradley & Bryant, 1983; Byrne & Fielding-Barnsley, 1995; Byrne, Fielding-Barnsley, & Ashley, 2000; Hatcher, Hulme, & Ellis, 1994; Kujala et al., 2001; Schneider, Küspert, Roth, & Visé, 1997; Temple et al., 2003; Torgesen et al., 2001; Torgesen et al., 1999; Törmänen & Takala, 2009; for a review including studies published 2000 – 2008, see Loo, Bamiou, Campbell, & Luxon, 2010; as well as reviews by Fletcher, Lyon, Fuchs, & Barnes, 2007; S. E. Shaywitz, 2003). There is far less research on other forms of intervention such as metacognitive strategies, which also have been shown helpful, especially in combination with phonological training (Lovett et al., 2000). Considering that a phonological core deficit is observed in the majority of poor readers, the emphasis on phonology-based interven-

tions is not surprising. Moreover, phonological deficits are the earliest indicators for troublesome reading. Ignorance until DD is undeniable, often referred to as the "wait-to-fail model", will most likely result in school failure (Daniel et al., 2006; S. E. Shaywitz et al., 2008). ICD-10 classification approves that scholastic, emotional, and behavioural problems are associated with DD. According to a national survey conducted in Switzerland in 2003, poor readers are in need of unemployment assistance almost three times more frequently than normal readers (Guggisberg, Detzel, & Stutz, 2007). The consequences thereof are nationwide economic costs clearly exceeding 1 billion Swiss Francs each year. Not unrelated, poor readers also are at risk for psychological unease. Low self-esteem has been reported in children and adults with dyslexia (Alexander-Passe, 2006; Julia M. Carroll & Iles, 2006; Edwards, 1994; Terras, Thompson, & Minnis, 2009). Anxiety, depression, or social withdrawal has been found increased in DD (Arnold et al., 2005; Julia M. Carroll & Iles, 2006; J. M. Carroll, Maughan, Goodman, & Meltzer, 2005; Riddick, Sterling, Farmer, & Morgan, 1999). Moreover, children with reading deficits exhibit antisocial (e.g., aggressive, delinquent) behaviour five times more likely than children of the remaining population (Rutter & Yule, 1970). It should be noted that a number of studies suggests that antisocial problems, in contrast to the internalizing problems, are entirely explainable by comorbidity with ADHD symptoms (Arnold et al., 2005; J. M. Carroll et al., 2005; Willcutt & Pennington, 2000). ADHD counts as the most common psychiatric concomitant of reading disabilities (Maughan & Carroll, 2006; S. E. Shaywitz, Fletcher, & Shaywitz, 1994).

Nevertheless, the economic and psychological costs of undiagnosed and untreated DD are substantial. Although there is no panacea for DD, early interventions have been shown effective and their permissive application should be encouraged. There is no harm for readers who do not meet any arbitrarily imposed cut-off diagnosis criteria, because reading is considered a dimensional ability (S. E. Shaywitz, Escobar, Shaywitz, Fletcher, & Makuch, 1992; Stanovich, 1988a) and those readers might still require and profit from special interventions.

1.3 Phonological Deficits as a Prevailing Account

Despite first definitions of DD 135 years ago (Kussmaul, 1877), none of the numerous theories on its aetiology forwarded since then is able to account for all cases of DD. These accounts include descriptions of core deficits in phonological processing, in rapid temporal processing, in cerebellar pathways, or in magnocellular pathways of the visual system. Deficits in rapid temporal processing have been suggested for the auditory modality (Tallal, 1980) or for both auditory and visual modalities (Farmer & Klein, 1995; Hari & Renvall, 2001; Van

Ingelghem et al., 2001). The cerebellar deficit theory states that impaired automatization of sensory-motor habits accounts for effortful reading (Nicolson & Fawcett, 1990; Nicolson, Fawcett, & Dean, 2001), based on evidence that children with DD sometimes have balance and motor-coordination problems under attention-demanding circumstances (Fawcett, Nicolson, & Dean, 1996; Haslum & Miles, 2007; Stoodley, Fawcett, Nicolson, & Stein, 2005). Magnocellular pathways that are dedicated to visual contrast sensitivity and to fast visual processing have also been suggested to be impaired in DD (Livingstone, Rosen, Drislane, & Galaburda, 1991; Lovegrove, Bwoling, Badcock, & Blackwood, 1980). This latter theory has been further developed into a comprehensive framework to explain and embed the other theories. Accordingly, magnocellular deficits not only affect the visual modality but also the auditory and sensorimotor domain and account for a general deficit in the processing of fast incoming sensory information (Stein, 2001). It is beyond the scope of this thesis to describe all of these accounts in detail. This chapter focuses on the phonological deficit – the most commonly observed impairment in dyslexia and the one of highest relevance in the present context.

1.3.1 The Phonological Deficit

In linguistics, 'phonology' refers to knowledge of the sound structure of words, as distinct from 'orthography' and 'semantics', which refer to knowledge of the letter combinations in written words and to conceptual knowledge required for comprehension, respectively (Price, 1998). The phonological deficit hypothesis refers to dysfunctional representations, storage and / or retrieval of phonemes, resulting in poor reading. It is the most widely accepted account of dyslexia for a number of reasons (e.g., Goswami, 2000; Ramus, 2003; S. E. Shaywitz & Shaywitz, 2005; Snowling, 2000; Vellutino, Fletcher, Snowling, & Scanlon, 2004). First, measures of phonological abilities consistently distinguish poor readers from typical readers (for studies in children, see Fletcher et al., 1994; Stanovich, 1988a; Stanovich & Siegel, 1994; for adults, see Bruck, 1992; Felton et al., 1990; for a review, see Wagner & Torgesen, 1987). Second, phonological abilities are a reliable predictor of future reading ease if assessed at preschool age (Mann, 1984, 1993; Share, Jorm, Maclean, & Matthews, 1984; Stanovich, Cunningham, & Cramer, 1984). Third, phonology-based trainings, designed to facilitate phonological awareness and letter–sound mapping, promote reading acquisition (see 1.2 Diagnosis and Significance, p. 2). Fourth, reading errors in dyslexia are primarily observed in languages where phonological processes are highly tapped, such as English with its ambiguous spelling-to-speech sound correspondences (Frith, Wimmer, & Landerl, 1998; Share, 2008). In

languages with a transparent correspondence, such as German, the deficit is primarily seen in reading speed (Wimmer et al., 2010).

Figure 1.1 depicts a simplified model of visual word recognition and reading aloud (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001). There is a variety of models on reading, but they generally share the concept of two processing routes: a lexical / semantic route (the upper route in Figure 1.1) and a nonlexical / phonological route (on the lower and right half). Nodes that tap phonological processing are in orange boxes. Obviously, beginning readers need to learn rules of grapho-phonological conversion for reading aloud. In order to eventually extract the meaning of unfamiliar letter strings, another two phonological processing nodes are engaged according to this model. Hence, phonology is specifically essential during learning to read. It has indeed been suggested that this initial handicap leads to a vicious circle that lets poor readers fall farther and farther behind as demands increase, whereas typical readers get better and better as they practice what they have learned (Stanovich, 1986, 1988b). Such a view is also in line with the effectiveness of even short phonological trainings in preschoolers at risk (Brem et al., 2010). Note that models of reading postulate the possibility of extracting semantics without phonological processes (in Figure 1.1, the route from the left directly to the top). However, it is more realistic to assume that in most readers, even the best ones, meaning is derived by an interaction of orthographic, phonological, and semantic representations (e.g., Coltheart et al., 2001; Plaut, McClelland, Seidenberg, & Patterson, 1996; Price & Devlin, 2011).

The more interesting question is which phonological processes exactly are impaired in DD. An intuitive idea is that phonological representations are degraded, that is, they are noisier or more transient, or they have less sharp boundaries (Elbr, 1998; Snowling, 2000). In contrast, Ramus and Szenkovits (2008) report a comprehensive series of experiments that led them to conclude that phonological representations are intact in DD, i.e., all phonetic features of language are correctly encoded. However, accessing these encodings is deficient under certain conditions that involve speeded or repeated retrievals (e.g., rapid automatized naming), storage in short-term memory (e.g., spoonerism task[2]), extraction from noise (e.g., degraded stimuli or noisy background), and other task difficulty factors. Still, the exact nature of the phonological deficit, if at the core of the problem at all, remains undefined at both theoretical and empirical levels.

[2] In this task the initial phonemes of word pairs have to be exchanged (e.g.: boat – fish into foat – bish; Perin, 1983).

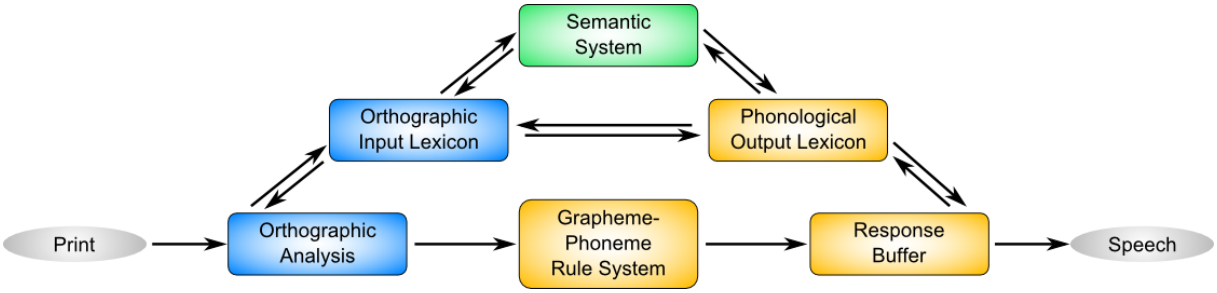

Figure 1.1 The dual-route cascaded model of visual word recognition and reading aloud (Coltheart et al., 2001).

1.3.2 Recent Advances Around the Phonological Deficit Hypothesis

Recent studies have made increasing empirical efforts to relate the phonological deficit to impairments in fluent print decoding.

For instance, a number of studies has focussed on the interaction of phonological and visual print decoding by simultaneously presenting phonemes to the auditory modality and graphemes to the visual modality. The two input modalities did either match or mismatch. Different brain responses between matching and mismatching conditions were taken as an indicator for audiovisual (AV) integration (Blau et al., 2010; Blau, van Atteveldt, Ekkebus, Goebel, & Blomert, 2009; Froyen, Willems, & Blomert, 2011; Mittag, Thesleff, Laasonen, & Kujala, 2012; Widmann, Schröger, Tervaniemi, Pakarinen, & Kujala, 2012). Based on these studies, it has been suggested that a specific deficit in AV integration and in the automated formation of grapho-phonological objects is at the core of the phonological deficit hypothesis (Blomert, 2011). The integration of concurrent sensory information across different modalities is a fundamental aspect of human perception (Kayser & Logothetis, 2007; McGurk & MacDonald, 1976) and represents an inherent process in reading. During the acquisition of reading skills arbitrary visual characters (graphemes) need to be mapped onto their corresponding sounds (phonemes) in order to understand the meaning. In dyslexia, the cross-modal binding deficit "may interfere with and/or slow down the incremental tuning of auditory and multisensory cortex for the fast integration of unique audiovisual orthographic–phonological objects" (Blomert, 2011, p. 702). A deficit in the formation of 'graphonemes' has previously been suggested by Whitney and Cornelissen (2005), but strong empirical evidence had been missing at that time. These authors also reasoned that the efficient formation of graphonemes eventually leads to gradual specializations to visual print stimuli within the left ventral occipitotemporal (vOT) cortex. These specializations are essential for efficient reading. Left hemi-

spheric vOT tuning to print by grapho-phonological expertise has repeatedly been suggested (McCandliss & Noble, 2003; Sandak et al., 2004; Schlaggar & McCandliss, 2007; Share, 1995). This hypothesis also receives strong support by studies showing left vOT activation increases with emerging reading skills (Ben-Shachar, Dougherty, Deutsch, & Wandell, 2011; Brem et al., 2010; B. A. Shaywitz et al., 2002), or after AV training games (Brem et al., 2010; Spironelli, Penolazzi, Vio, & Angrilli, 2010).

There have been numerous studies during the past decade that focussed on the exact contributions of the left vOT cortex to reading. With respect to dyslexia, this region has robustly been shown underactivated (for a meta-analysis, see Richlan, Kronbichler, & Wimmer, 2011), in line with the concept of a phonologically-guided region. In addition, lesions at this site may lead to acquired dyslexia or letter-by-letter reading with speech comprehension or production being spared (Binder & Mohr, 1992; Cohen et al., 2004; Cohen et al., 2003; Dejerine, 1891; Gaillard et al., 2006; Leff et al., 2001; Starrfelt, Habekost, & Gerlach, 2010; Starrfelt, Habekost, & Leff, 2009; Warrington & Shallice, 1980). Thus, the critical involvement of vOT regions in visual letter string processing is beyond question and it is most likely that an efficient print tuning of this region accounts for fluent reading (e.g., B. A. Shaywitz et al., 2002). This, however, does not mean that phonological processes become obsolete in fluent readers. Current models of reading (see above) do suggest reduced phonological reliance with increasing fluency but still claim the highly interactive nature of reading (Coltheart et al., 2001; Plaut et al., 1996). Recently, an interactive role in reading has repeatedly been suggested for the left vOT cortex (Mano et al., 2012; Price & Devlin, 2011; Richardson, Seghier, Leff, Thomas, & Price, 2011). Hence, this phonologically tuned region seems to constitute an important interface where information extracted from visual stimuli makes contact with linguistic processes (Cai, Paulignan, Brysbaert, Ibarrola, & Nazir, 2010; Posner & Carr, 1992).

To summarize, the importance of AV or grapho-phonological interactions for the aetiology of dyslexia has grown from two lines of evidence: Firstly, recent evidence suggests impaired AV integration in dyslexic children (Blau et al., 2010; Froyen et al., 2011; Widmann et al., 2012) as well as adults (Blau et al., 2009; Mittag et al., 2012). Secondly, robust underactivation has repeatedly been shown for the left vOT cortex, a region whose dysfunctionality has been regarded as the consequence of impaired grapho-phonological conversion and whose functional contributions to reading have been related to the matching of bottom-up visual and top-down phonological (or linguistic in general) input.

2 Aims of the Thesis

The first study emanates from the hypothesized role of the left vOT cortex as an interface for visual and phonological processing streams. The aim was to replicate the well-documented underactivation of this region in dyslexia in a context of no explicit and minimized phonological demands. Even if the functional role of left vOT regions is highly associated with visual print processing, modulatory or re-entrant effects of, for instance, phonological operations are likely (Price & Devlin, 2011; Richardson et al., 2011; Twomey, Kawabata Duncan, Price, & Devlin, 2011). These complex interrelations of different processing stages may critically limit interpretations of left vOT underactivation in DD as primarily an orthographic coding deficit. Underactivation might rather be confounded by impairments in phonological processing if the task requires such processing. This has usually been the case (see 4.2 Introduction, p. 16). If probed in the context of minimized phonological demands, however, underactivation would provide important evidence that efficient visual print tuning has failed in dyslexic adolescents and that deficient tuning might be the proximate marker of impaired reading in the matured brain. This would be in line with the hypothesis of a phonologically guided left vOT tuning during reading acquisition and a failure of such guidance and tuning in dyslexia. A further aim of this study was to investigate whether print tuning is impaired at the level of single letters, letter strings, or whole words, which still is an unresolved issue in the literature.

Having probed the existence of visual print tuning deficits under minimized grapho-phonological demands, the second study went back to investigate more closely the exact nature of grapho-phonological or AV deficits in dyslexic adolescents. Audiovisual deficits have so far been shown for children and adults, but not for adolescents (see previous section, p. 7f). Considering that only one previous study has provided evidence that AV deficits might not be restricted to the domain of grapho-phonological (letter–speech sound) conversion but rather be more general in nature, one main aim of the study was to test the generalizability and the level of AV deficits in dyslexia. We built upon previous designs but included additional conditions to test more basic and sensory dimensions of AV integration. Alternatively, it is also possible that AV deficits are confined to impairments in grapho-phonological conversion. We therefore also tested whether deficits are specifically seen at the level of phonetic content in a naturalistic context of speech- and word-like stimulation. A more detailed description of theoretical background and particular aims follows in the introductory sections of the studies.

The two studies investigated the neural basis of dyslexia in participants at a critical developmental stage, that is at the end of compulsory schooling where reading proficiency is still

trained at a high level before literacy experiences diverge due to different professional tracks. We believe that this represents a highly interesting and critical age for investigating the functional characteristics of the left vOT cortex on the one hand, and the exact nature of AV deficits on the other hand.

In this endeavour, fMRI and EEG data were acquired simultaneously in order to obtain a comprehensive picture of aberrances in dyslexia and to make use of the advantages of both techniques, especially the high temporal resolution of EEG and the high spatial resolution of fMRI. Readers familiar with both acquisition techniques may want to skip the next section that briefly describes principles as well as advantages and disadvantages of both techniques.

3 A Short Introduction to Neuroimaging Techniques

3.1 Electroencephalography

Electroencephalography (EEG) measures electrical brain activity by means of electrodes that are mounted on the scalp surface. These electrodes detect voltage fluctuations relative to a reference electrode. The fluctuations primarily reflect electric currents of summed postsynaptic potentials of pyramidal neurons. Specifically, excitatory postsynaptic potentials induce an inflow of Na+ at basal dendrites, thereby producing an active sink of current. Given that neurons behave like distinct physical entities that maintain electrical neutrality, an active source of current emerges at opposite, apical regions of the neuron. This way, the neuron forms a current dipole. The dipole induces (by means of volume conduction) passive currents in the surrounding tissue and eventually at the scalp surface. However, only if large amounts (at least thousands) of neurons are spatially aligned and fire synchronously, voltage changes become detectable at the scalp. Electrical currents produced by action potentials along the membrane are not detected by EEG because they are typically not synchronized and therefore cancel (Luck, 2005; Michel, Koenig, Brandeis, Gianotti, & Wackermann, 2009).

One way to further investigate the spontaneous voltage fluctuations is the separation into different frequency spectra reflecting neural oscillations. Oscillations inform about different brain states (e.g., sleep- or wakefulness) and aberrances in these oscillations are important for diagnosis of neurological conditions such as epilepsy.

In cognitive neurosciences, however, the event-related potential (ERP) technique is prevailing. Here, the EEG signal is time-locked to the onset of an external stimulus (of e.g. visual, somatosensory, or auditory nature). During the course of an experiment each stimulus condition is presented repeatedly and by means of averaging across these single trials the ERP becomes visible, whilst random noise cancels out. ERPs inform about the time-course of stimulus processing. Early ERP deflections primarily reflect physical properties of the stimulus and are called exogenous components, whereas later deflections after around 250 ms are dominated by cognitive processes and are referred to as endogenous components. Components are named according to their polarity and latency. For instance, a visual P1 is the first positive deflection in visual stimulus processing and commonly occurs around 100 ms after stimulus onset. The amplitude of components allows for comparisons across conditions or groups. In the context of print processing, the N1 is the first negative deflection occurring around 170 – 200 ms post stimulus (therefore also labelled N170, e.g., Bentin, Mouchetant-Rostaing, Giard,

Echallier, & Pernier, 1999; or N200, e.g., Allison, McCarthy, Nobre, Puce, & Belger, 1994). It has repeatedly been regarded as the earliest marker of print tuning (Allison, Puce, Spencer, & McCarthy, 1999; Bentin et al., 1999; Maurer, Brandeis, & McCandliss, 2005; Maurer, Brem, Bucher, & Brandeis, 2005; Nobre, Allison, & McCarthy, 1994; Tarkiainen, Helenius, Hansen, Cornelissen, & Salmelin, 1999).

Advantages and Disadvantages

EEG directly reflects neural activity. It counts as the "gold standard" with respect to temporal resolution, allowing continuous online imaging of brain activity. Measurements are inexpensive, silent, and non-invasive. Relatively few equipment is needed, facilitating measurements in various environments (e.g., in the field or in the magnetic resonance imaging scanner).

A disadvantage of EEG is its low spatial resolution and coverage. As already described, only synchronous activation of large and spatially aligned neural clusters is detected. EEG is most sensitive to clusters of neurons that are located closely and radially to the skull. Tangentially oriented or subcortical sources contribute far less to the EEG signal. Spatial resolution is further distorted by high resistance of the skull where expanding electric currents tend to spread laterally rather than radially. Moreover, a unique source localization of EEG signals is mathematically impossible, given that each activation pattern at the scalp may be produced by an infinite number of generator distributions (the so-called inverse problem; Helmholtz, 1853). Another caveat of EEG is the rather poor signal-to-noise ratio. Noise may stem from technical artefacts (e.g., line voltage) as well as from muscle tension or movements (e.g., tension at the forehead or eye movements). Last, subject preparation takes considerable amounts of time, depending on the system used und the number of electrodes to be mounted.

3.2 Functional Magnetic Resonance Imaging

Unlike EEG, functional magnetic resonance imaging (fMRI) does not directly measure neural activity. Functional MRI detects a signal that is dependent on the oxygenation level of blood flow in the brain (Ogawa, Lee, Kay, & Tank, 1990). Specifically, oxygenated and deoxygenated molecules (haemoglobin) have different magnetic properties, which enables the characterization of brain regions as a function of their oxygenation level. The coupling between oxygen consumption and neuronal activity is widely acknowledged and has especially been proven for local field potentials (this is the terminology for postsynaptic potentials in intracellular recordings; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Logothetis & Wandell, 2004). Neural firing leads to an initial reduction in oxygen and glucose levels,

followed by increased blood flow in surrounding blood vessels that peaks after around 5 – 8 seconds and compensates for the momentary consumption. In fact, whereas glucose supply does appear to match consumption, oxygen supply overcompensates consumption. Hence, the signal increase is – counterintuitively – based on increased oxygen levels after neural activity. Reasons for the oxygen oversupply are still a matter of debate (Logothetis & Wandell, 2004). The so-called hemodynamic response function (HRF) describes the course of the blood oxygenation level dependent (BOLD) response (Figure 3.1). When blood flow returns to baseline, an initial undershoot in the response is sometimes observed. Complete recovery takes approximately 15 to 20 seconds, depending on the experimental task.

Event-related fMRI follows exactly the same logic as is used in ERP, where signals are time-locked to the onset of a stimulus.

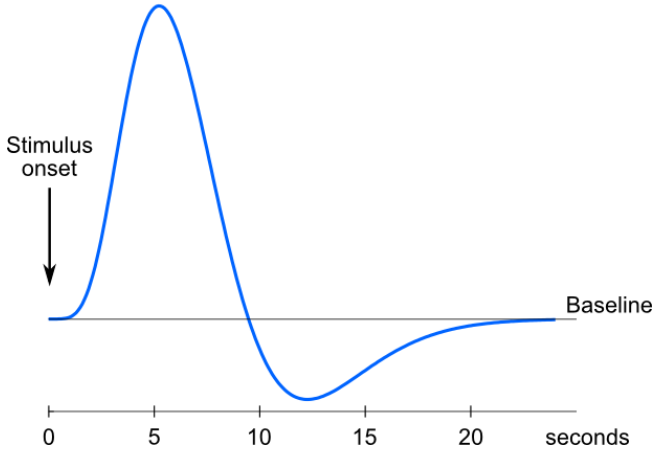

Figure 3.1 The hemodynamic response function

Advantages and Disadvantages

Functional MRI is a non-invasive method and can therefore repeatedly be applied to participants or patients. Among the most advantageous aspects of fMRI is its good spatial resolution of commonly around 3 mm^3 (resolution increases with higher magnetic field strength of scanners). Spatial resolution can be further improved by coregistration of fMRI images with in-session high resolution anatomical scans. Coverage from specific target regions to whole brain recordings is possible. Scanners are widely available in developed nations.

A disadvantage of fMRI is its low temporal resolution (> 1 s), which is owed to the sluggishness of the BOLD response. Unlike in EEG, online imaging of mental operations is not possible and neural activity is not directly measured. Moreover, the BOLD signal is a relative measure, only meaningful in comparison of two brain states (e.g., task accomplishment versus

resting blocks). As in EEG, activation does not imply a causal contribution to task performance. Rather, inferences about an area's functional contribution are needed.

4 Study 1: Visual Print Tuning Deficits in Dyslexic Adolescents Under Minimized Phonological Demands

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4.1 Summary

The left ventral occipitotemporal cortex is reliably activated by visual orthographic stimulation and has repeatedly been found underactivated in developmental dyslexia. However, previous studies have made little effort to specifically probe orthographic processing while minimizing the need for higher-order reading related operations, especially phonological processing. Phonological deficits are well documented in dyslexia but may limit interpretations of ventral occipitotemporal underactivation as a primarily orthographic coding deficit, considering that different processing modes occur highly parallel. We therefore used a task that restricts higher-order processing to better isolate orthographic deficits. Thirteen dyslexic adolescents and twenty-two matched typical readers performed a low-level target detection task combined with rapidly presented stimuli of increasing similarity to real words during functional magnetic resonance imaging. The clear deviance found in impaired readers' left ventral occipitotemporal organization suggested deficits in print sensitivity at bottom-up processing stages that are largely independent of phonological operations. This finding elucidates print processing during a critical developmental transition from child- to adulthood and extends current accounts on left ventral occipitotemporal functionality.

4.2 Introduction

Developmental dyslexia is a learning disability of neurobiological origin with substantial familial and genetic risk (Pennington & Olson, 2008; Schulte-Körne, Warnke, & Remschmidt, 2006). It is characterized by specific impairments in the acquisition of efficient reading, often accompanied by spelling difficulties. Impairments emerge despite conventional instruction, adequate intelligence and motivation (Lyon et al., 2003). DD is one of the most widespread disorders, affecting around 5% of school-aged children (Schulte-Körne, 2010; Schulte-Körne & Remschmidt, 2003). Converging evidence from neuroimaging studies in DD points to both structural and functional deficits in brain regions involved in reading, including inferior frontal, temporal, as well as parieto- and occipitotemporal regions of mainly the left hemisphere (Jobard, Crivello, & Tzourio-Mazoyer, 2003; Richlan, Kronbichler, & Wimmer, 2009; Richlan et al., 2011; Temple, 2002; Vigneau et al., 2006). The left vOT cortex has received increasing attention in dyslexia research (e.g., Richlan et al., 2011) given its robust response to orthographic stimulation in typical readers (e.g., Baker et al., 2007; Ben-Shachar et al., 2011; Cohen et al., 2002; Dehaene, Le Clec, Poline, Le Bihan, & Cohen, 2002; Kronbichler et al., 2004; Vinckier et al., 2007; for a review, see Wandell, 2011) and given that lesions at this site may lead to alexia (Cohen et al., 2003; Dejerine, 1891; Starrfelt et al., 2009). Thus, this region is functionally associated with orthographic processing and coding, which in the present context refer to the visual (bottom-up) aspect of print processing, in contrast to phonological or semantic processing, which involve the access to the sound structure or the conceptual knowledge needed for understanding of words, respectively. The present conceptualization of orthographic coding comprises both coarse and fine print tuning based on our previous developmental work (e.g., Brem et al., 2009; Maurer, Brem, et al., 2005; Maurer et al., 2006). Coarse neural tuning of left vOT regions has been found for single letters or letter strings when contrasted with pseudofont or symbol strings (Baker et al., 2007; Brem et al., 2006; Brem et al., 2009; Maurer, Brem, et al., 2005; Maurer et al., 2006; Xue & Poldrack, 2007), while fine-tuning refers to the sublexical and whole word levels (Binder, Medler, Westbury, Liebenthal, & Buchanan, 2006; Dehaene, Cohen, Sigman, & Vinckier, 2005; Glezer, Jiang, & Riesenhuber, 2009; Kronbichler et al., 2004; Vinckier et al., 2007) as for example reflected by orthographic measures of regularity like bigram (letter-pair) frequency. To further elucidate the level of vOT functionality and dysfunction in dyslexia is one main aim of the present study, as described below.

Importantly, left vOT regions have repeatedly been shown underactivated in dyslexic children (Maurer et al., 2007; Schulz et al., 2009; B. A. Shaywitz et al., 2002; van der Mark et al., 2009), adolescents and adults (Brambati et al., 2006; Brunswick, McCrory, Price, Frith, & Frith, 1999; Helenius, Tarkiainen, Cornelissen, Hansen, & Salmelin, 1999; Hoeft et al., 2007; McCrory, Mechelli, Frith, & Price, 2005; Paulesu et al., 2001; Richlan et al., 2010; Salmelin, Service, Kiesila, Uutela, & Salonen, 1996; Wimmer et al., 2010), with more extended underactivation in adults compared to children (for a meta-analysis, see Richlan et al., 2011).

However, with only one exception (Helenius et al., 1999) all of these studies explicitly or implicitly left ample opportunity to process presented letter strings in a phonological manner in addition to orthographic processing. Even if the functional role of left vOT regions is highly associated with orthographic processing, modulatory or re-entrant effects of, for instance, phonological processing are likely (Price & Devlin, 2011; Richardson et al., 2011; Twomey et al., 2011). Thus, findings of dyslexic vOT underactivation might at least in part be caused by phonological deficits, given that impaired learning of spelling–sound associations represents one of the core deficits in DD (Goswami, 2000; Ramus et al., 2003; S. E. Shaywitz & Shaywitz, 2005; Snowling, 2000; Vellutino et al., 2004). Hence, if task-related phonological processing is not reduced to a minimum, the complex interrelations of different processing stages in print processing may indeed limit interpretations of left vOT underactivation in DD as primarily an orthographic coding deficit.

In the present study, we adopted a task design intended to "restrict as much as possible top-down effects which can modulate or even reverse activation patterns in the visual cortex" (Vinckier et al., 2007, p. 144), and building on evidence that vOT regions may particularly be probed by rapidly presented stimuli (Mechelli, Friston, & Price, 2000; Price, Moore, & Frackowiak, 1996). The present task therefore combines short stimulus duration (yet clearly above perception threshold) at high presentation rate with a low-level detection task as in Vinckier et al. (2007). While such a framework will reduce task-related and deliberate higher-order processes, task-unrelated automatic phonological and semantic access as advocated by current models of reading (Price & Devlin, 2011) will hardly be entirely suppressed. For instance, even subconsciously presented priming stimuli that share phonological and / or conceptual aspects with a subsequent target stimulus suffice to modify BOLD responses to those targets in left vOT regions (Kherif, Josse, & Price, 2011). On the other hand, there are also priming studies that emphasize the importance of task context even for subconscious phonological and semantic processes (Nakamura, Dehaene, Jobert, Le Bihan, & Kouider, 2007; Norris & Kinoshita, 2008). For instance, Nakamura et al. (2007) found the task set to influ-

ence which brain region showed response modulation by subconsciously perceived primes, suggesting that voluntary task control can affect involuntary, automatic processing. Hence, the present non-linguistic task might contribute to a reduction of automatic higher-order processes, although this cannot be determined with certainty. Taken together, we believe that this task provides an interesting framework for reliably probing vOT print sensitivity whilst reducing deliberate and possibly also automatic higher-order processes.

Four types of stimuli with increasing similarity to real words are used: (1) false font strings, (2) strings containing rare bigrams (i.e., pairs of letters that rarely adjoin), (3) strings containing frequent bigrams, (4) real words. Vinckier et al. (2007) observed a left vOT posterior to anterior gradient of increasing orthographic specialization indicating that visual processing of real words activates more anterior vOT portions than, for example, rare bigrams or symbol strings. They concluded that the left vOT cortex becomes attuned to orthographic regularities during reading skill acquisition. Hence, it was hypothesized that in our adolescent sample (a) nonimpaired readers exhibit such a posterior to anterior gradient of increasing print sensitivity; and (b) that impaired readers lack such gradual specializations in this brain region (van der Mark et al., 2009). If true, we provide evidence that vOT dysfunctions in DD are relatively independent of the well-established phonological core deficit. Insights about vOT characteristics in adolescents are particularly valuable given that previous evidence is sparse and that they may contribute in clarifying the largely unresolved transitions from child- to adulthood in these regions (Richlan et al., 2011).

4.3 Methods

4.3.1 Participants

A total of 45 adolescents was recruited by the end of 9th grade, the last grade of compulsory schooling in Switzerland (Table 4.1). All were part of a longitudinal panel either tracked since kindergarten (~75% of participants) or since 5th grade (Maurer et al., 2007; Maurer, Bucher, Brem, & Brandeis, 2003; Maurer et al., 2011; Schulz et al., 2008; Schulz et al., 2009). According to current and 5th grade reading scores, 22 adolescents were assigned to a nonimpaired reading group and 13 were categorized as reading-impaired (see below). The 8 participants falling in between these groups were only included in correlation analyses. One participant was excluded due to technical problems during recording, another one due to ADHD comorbidity (see below). Participants reported normal or corrected-to-normal vision. All were

native speakers of (Swiss-) German. Nonverbal IQ fell in the range of ± 1 SD, except in one control subject (nonverbal IQ = 75; all critical statistical analyses were repeated firstly with nonverbal IQ as covariate and secondly after exclusion of this participant, leading to the same results). Adolescents and their parents gave informed written consent upon participation. The study was approved by the local ethics committee.

Table 4.1 Demographic characteristics of control and dyslexic participants (number or M ± SD) and group differences (*t*-tests or Fisher's exact test)

	Control	Dyslexic	*P*-value
n	22	13	–
Age (years)	15.9 ± 0.5	16.1 ± 0.7	n.s.
Sex (male:female)	10:12	8:5	n.s.
Handedness (right:left:ambidextrous)	18:4:0	10:2:1	n.s.
Handedness continuous	57.6 ± 68.0	48.8 ± 61.4	n.s.
Estimated verbal IQ	112 ± 10	108 ± 17	n.s.
Estimated nonverbal IQ	110 ± 14	107 ± 11	n.s.
Estimated working memory	101 ± 13	85 ± 11	$P < 0.001$
Correctly read words/min			
currently (9th grade)	115.8 ± 11.2	82.9 ± 13.1	$P < 0.001$
5th grade	95.2 ± 13.7 (n=21)	49.1 ± 8.6 (n=12)	$P < 0.001$
Correctly read pseudowords/min			
currently (9th grade)	76.3 ± 13.4	44.9 ± 7.5	$P < 0.001$
5th grade	56.3 ± 9.7 (n=21)	30.3 ± 3.7 (n=12)	$P < 0.001$
Sentence processing speed	38.0 ± 7.6	25.8 ± 6.0	$P < 0.001$
Spelling errors	14.4 ± 9.7	38.4 ± 7.2	$P < 0.001$

M = mean, SD = standard deviation.

Screening for neurological diseases or psychiatric disorders indicated attention deficits / hyperactivity in one dyslexic female according to parents (Child Behavior Checklist, Achenbach, 1991) and self rating (Strengths and Difficulties Questionnaire, Klasen, Woerner, Rothenberger, & Goodman, 2003). This participant was excluded from all analyses (although core results remained significant if included). In order to assess reading level, subjects were tested for current word and pseudoword reading fluency (Salzburger Lesetest II, SLRT II, Moll & Landerl, 2010), sentence processing speed (Salzburger Lesescreening, SLS, Auer, Gruber, Mayringer, & Wimmer, 2005), and spelling ability (Rechtschreibungstest, Kersting & Althoff, 2004). In 5th grade, 15 participants had scored below 10% in word or pseudoword reading. Given that at present only 7 of them still had reading difficulties to this extent, we

classified as dyslexic those that 1) scored below 10% in at least one subtest of SLRT II at 5th grade and 2) scored below 20% of a norm group (see paragraph below) in at least one subtest of SLRT II or SLS at present. Participants that fulfilled just one of these two criteria were not assigned to any group but were entered in correlation analyses only. Participants were assigned to the control group if their reading skills in current and 5th grade assessments were above the 20th percentile. Two subjects had refused participation in 5th grade. One of them could clearly be assigned to the dyslexic group (below 5th percentile in all current reading tests), the remaining adolescent joined the control group.

Because appropriate age norms were not available for the reading tests used, scores were compared to norms based on a group of 71 adolescents (mean age 15.8 ± 0.6 years), who had received continuous schooling in German and who had at least one native (Swiss-) German speaking parent. This group was recruited from local schools and was representative for the canton of Zurich in level of education.

Current IQ scores were quantified by means of the HAWIK-IV subtests block design, similarities, and digit span (Petermann & Petermann, 2007), which were used to estimate nonverbal IQ, verbal IQ, and working memory, respectively. Groups matched in age, sex, handedness (Oldfield, 1971), nonverbal, and verbal IQ (Table 4.1).

4.3.2 Stimuli and Task

Four stimulus categories of increasing similarity to German words were devised: (1) false font strings (FF), (2) strings containing rare bigrams (RB, i.e., pairs of letters that rarely adjoin), (3) strings containing frequent bigrams (FB), (4) German nouns (W). All stimuli consisted of five characters and started with a capital, which is compulsory in German nouns. Each category was represented by a set of 40 different stimuli. All letter string conditions (i.e., RB, FB, W) had the same ratio of letter occurrence. The RB condition exhibited a minimized mean aggregated bigram frequency (M = 2967 ± 1215), whereas FB (M = 16266 ± 5131) exhibited an overall bigram frequency like W (M = 16158 ± 6760, see Figure 4.1B). Aggregated bigram frequency ranged from 753 (RB stimulus “Bgdae”) to 33419 (W stimulus “Eisen” [=iron]). These construction criteria resulted in most FB stimuli being fully pronounceable, whereas RB stimuli were hardly pronounceable (see supplemental Table 4.4, p. 47, for a full listing of stimulus sets). German nouns were taken from all levels of frequency of occurrence (per one million words) with a mean of 68 ± 102. The false font list consisted of character strings matched for basic physical properties of letters. The ratio of different characters used was the same as in the other lists. For details on stimulus construction, see the supplementary material

(p. 40). All stimuli were presented in the centre of the field of view on a screen illuminated by a rear projector. They were black on white background and extended over a horizontal visual angle of approximately 4.1 degrees.

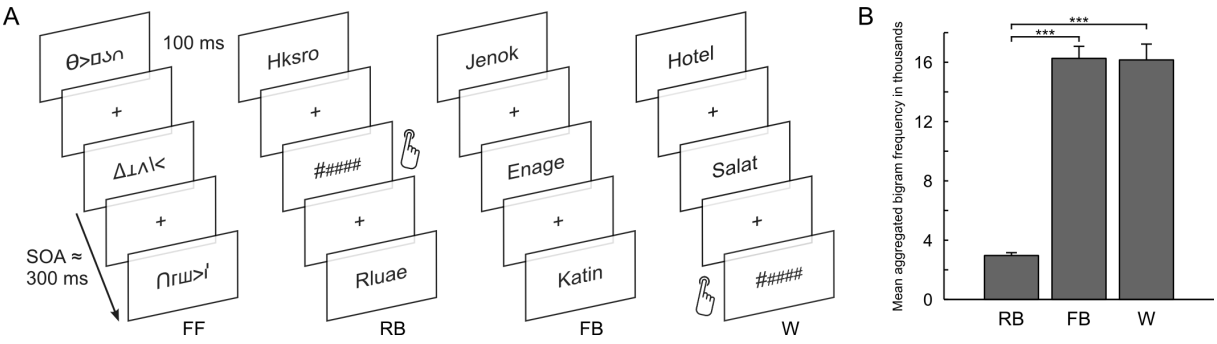


Figure 4.1 Experimental design and example stimuli (A). In a rapid serial visual stimulation paradigm (stimulus duration = 100 ms, SOA ≈ 300 ms), participants had to detect target stimuli (strings of hash keys) embedded into blocks presenting 4 conditions of approximations to real words. B) Comparison of mean aggregated bigram frequencies of the letter string conditions (*$P < 0.001$). Abbreviations: FF = false fonts, RB = rare bigrams, FB = frequent bigrams, W = words, SOA = stimulus onset asynchrony.**

Blocks of 20 stimuli alternated with resting blocks of 4, 6, or 8 seconds (M = 6 s). Within blocks of stimulation, all stimuli were shown for 100 ms. Offset-to-onset interstimulus interval jittered in the range of 150 ms to 250 ms with a mean of 200 ms to enhance the quality of simultaneously recorded EEG signals (see below). The order of stimuli within blocks was pseudorandomized, making sure that character repetitions in consecutive strings were minimized and that no character was ever repeated at the same position in consecutive strings (following Vinckier et al., 2007). Ordering of blocks was also pseudorandomized with never more than one immediate repetition of the same string condition. Sixteen blocks were presented per condition, resulting in 320 stimuli per condition and 8 repetitions of each stimulus. Repetitions were evenly distributed across the session. A central cross hair was visible whenever there was no stimulus.

To ensure that participants stayed focused, rare target stimuli had to be detected by button press (see Figure 4.1A). In all conditions, half of the blocks were interspersed with one target at a random position (except for the first five positions of a block). Subjects were familiarized with the task outside of the scanner und were instructed to fixate the cross hair at all times and to detect targets as quickly as possible.

4.3.3 Behavioural Data

A button press occurring between 100 ms and 2000 ms after target onset counted as a hit. Accuracy (hit rate) was compared between conditions and groups using Fisher's exact tests. Reaction time was analysed by a repeated measures ANOVA with the within-subject factor stimulus type (FF, RB, FB, W) and the between-subject factor group (dyslexic, control).

4.3.4 fMRI Acquisition and Analysis

MRI data was acquired on a 3.0 T (GE Healthcare) whole-body scanner. For functional imaging data, 466 images with 33 axial slices covering the whole brain were acquired using a T2*-sensitive echo planar imaging (EPI) sequence (TR = 1.815 s; flip angle 75°; TE = 32 ms; FOV = 24 cm; matrix = 64 x 64; slice thickness = 3.3 mm; gap = 0.5 mm; in-plane resolution = 3.75 x 3.75 mm; SENSE factor = 2). The first four scans were discarded due to scanner equilibration effects. A high-resolution T1-weighted anatomical image was acquired for each subject (SPGR sequence, 172 axial slices, slice thickness = 1 mm, in plane resolution = 1 x 1 mm, TR = 9.972 ms; flip angle 8°; TE = 2.912 ms; matrix = 256 x 204).

Participants were provided with earplugs, and custom-made padding was used for head stabilization and further acoustic insulation. No subject exceeded a volume-to-volume threshold for head movement of >± 2 mm translation or >± 2° rotation.

Functional MRI data preprocessing and statistical analysis was done using SPM8 (Wellcome Trust Centre for Neuroimaging, London, http://www.fil.ion.ucl.ac.uk/spm/). Data were motion corrected and coregistered to the bias corrected anatomical scan. The DARTEL approach (Ashburner, 2007) was taken for normalizing and smoothing (8 mm FWHM) the data (according to SPM8 manual, Ashburner et al., 2010). Within this approach, a custom template is created based on segmented anatomical scans of all participants as well as flowfields that parameterise the deformations of each subject to this template. The template and flowfields are then used for spatial normalisation. As a result, functional volumes with the default sampling of isotropic 1.5 mm^3 voxels in MNI (Montreal Neurological Institute) space were obtained.

Statistical analysis of fMRI data was carried out in a two stage mixed effects model. At the subject level, stimulation blocks were modelled as 6 seconds events and targets as punctual events using the standard SPM hemodynamic response function and its time derivative. Individual realignment parameters were entered into the regression model. Data were temporally high-pass filtered with a frequency cut-off period of 128 seconds, and serial correlations were

accounted for using a first order autoregressive model. These analyses were repeated with stimulus repetition as a parametric modulator (taking values from 1 to 8), given that this might have an influence on BOLD activity during the course of a measurement (e.g., Katz et al., 2005; Pugh et al., 2008). All findings presented here remained unchanged after accounting for repetition effects, as will be reported more thoroughly in the discussion.

At the group level, voxelwise whole brain random effects analyses and region of interest (ROI) analyses were conducted. Whole brain effects were assessed by means of a flexible factorial design with the factors subject, group, and stimulus type. Unequal group sizes were accounted for by selecting unequal variance for the group factor. Regressors of all main effects and of the group by stimulus type interaction were entered into the design matrix. Statistical mappings are depicted at a $P < 0.005$ significance level, corrected for multiple comparisons using a cluster extent threshold ($k \geq 160$, equivalent to a volume of 540 mm^3). This corresponds to a cluster-level correction for multiple comparisons at the $P < 0.05$ level. The voxel extent threshold was the result of Monte Carlo simulations (Slotnick, Moo, Segal, & Hart, 2003) that were run with a conservative estimate for the smoothness of data (8 mm FWHM, as used for smoothing of functional scans) in order to avoid type II error.

Regions of interest within the vOT cortex were derived according to Vinckier et al. (2007). At predefined Y coordinates (Y = -96, -80, -64, -56, -48, -40) each ROI (spheres with 4 mm radius) was centred on the maximum voxel of the *F*-test representing the main effect of stimulus type (see Vinckier et al., 2007, for details). This procedure was done separately for both left and right hemispheres and worked well if the main effect of the control group was used, but less so if the main effect of the dyslexic group was used. Specifically, the dyslexic sample exhibited for the anterior ROIs highest *F*-values at locations lying up to 22 mm more medially than coordinates in Vinckier et al. (2007) and extending to cerebellar regions. Hence, we constrained the search by centring a square (10 x 10 mm) upon each ROI defined by Vinckier et al. (2007). Results reported here are based on ROIs derived in this constrained way using the entire sample's main effect of stimulus type. In addition, all analyses were repeated with two sets of ROIs based on each groups' main effects, leading to the same critical significances and interpretations.

The mean percent signal change was computed within each ROI using MARSBAR on the smoothed data (http://marsbar.sourceforge.net, Brett, Anton, Valabregue, & Poline, 2002). A repeated measures ANOVA with the within-subject factors hemisphere (left, right), ROI (ROI 1, 2, 3, 4, 5, 6 from anterior to posterior), stimulus type, and between-subject factor group was done to test our main hypotheses. The existence of a gradient of increasing word sensitivity

was examined in all ROIs by means of linear trends across all four conditions as well as across the three letter string conditions only. Post-hoc *t*-tests were also done.

To investigate further effects of the whole brain analyses, additional ROIs (spheres with 4 mm radius) were centred on the peaking voxel of significant clusters. Two ROIs were also placed on the bilateral lingual peaks of the entire's sample main effect of stimulus type. These ROIs were analysed similar to the vOT ROIs. In all ANOVAs *P*-values were Greenhouse-Geisser corrected whenever sphericity assumptions were violated. ANOVAs and post-hoc *t*-tests were reliable despite unequal group sizes, because variances were homogenous across groups and data were approximately normally distributed according to standard tests implemented in SPSS (Version 20.0, IBM Corp.).

4.3.5 EEG Acquisition and Analysis

Simultaneous EEG data were acquired inside of the scanner using MR-compatible 64 channel caps. Further information on methods and results may be found in the supplementary material. In short, EEG data, and particularly the analyses of P1 and N1 component of the ERP failed to reveal converging evidence, or robust and remarkable additional insights despite good data quality and robust topographies and task effects.

4.4 Results

4.4.1 Behaviour

Target detection accuracy was not significantly affected by stimulus type in neither group (both $P > 0.8$). Accuracy did not differ significantly between groups for the W, FB, and RB conditions (all $P > 0.4$), but there was a trend in the FF condition ($P < 0.1$) with lower accuracy in dyslexics. Pooled across conditions, overall accuracy was 98.2% in nonimpaired and 96.6% in impaired readers.

Analysis of reaction times revealed a main effect of group ($F(1,33) = 17.22$, $P < 0.001$), no main effect of type and no type by group interaction. Overall mean reaction time was 469 ms in nonimpaired and 530 ms in impaired readers. Mean reaction time correlated with word ($r = -0.517$, $P < 0.01$) and pseudoword reading fluency ($r = -0.581$, $P < 0.001$).

4.4.2 Whole Brain Analyses

Contrasts of each condition against rest revealed the expected vOT activation patterns. Activation to words across all adolescents is shown at the top of Figure 4.2 (see Table 4.5 of supplements, p. 48, for a listing of activation clusters to all conditions). Main effects of stimulus type arose in large right fusiform clusters in both groups. Left fusiform and more lateral vOT

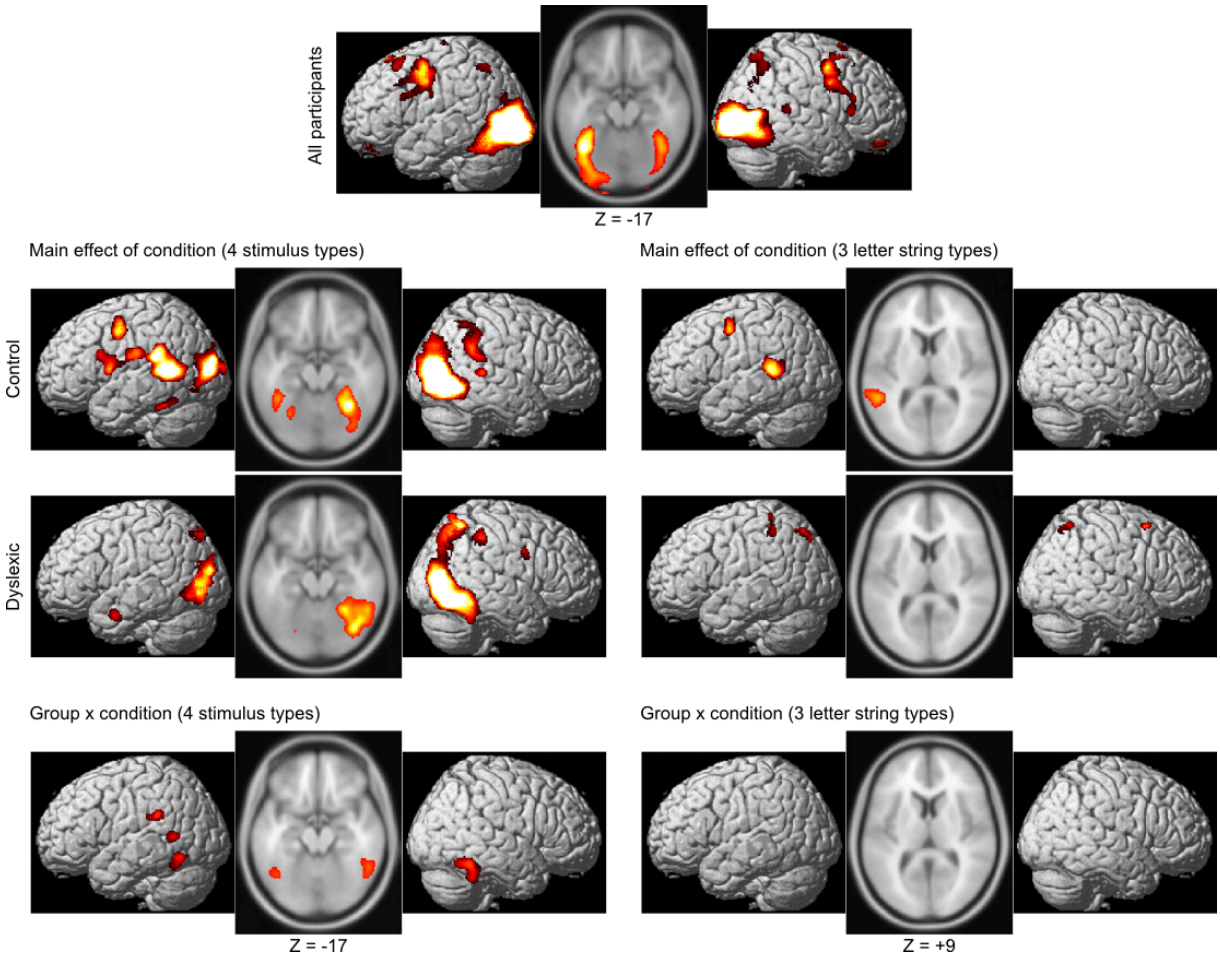


Figure 4.2 Whole brain effects. Brain renders and axial section views of activation to words minus rest (top row) and results of ANOVAs testing the main effects of condition for both groups (rows 2 – 3) with and without the false font condition (left and right panel, respectively). The bottom row shows interactions of group and condition. Threshold at $P < 0.005$ voxelwise, cluster extent $k \geq 160$.

effects were evident in controls but very limited or absent in dyslexics. In controls, stimulus type also had an influence on the left middle-to-superior temporal gyrus and anterior regions extending into precentral regions. The left posterior superior temporal gyrus (STGp) also showed up when only the three types of letter strings were compared. STGp or more anterior clusters were not found in dyslexics. Testing the group by stimulus type interaction revealed posterior middle temporal (MTGp) and inferior parietal lobule (IPL) clusters, as well as a

right cerebellar cluster located in Crus I. Importantly, left and right vOT clusters became significant (also see supplementary Table 4.6, p. 49). The left cluster fell into the range of our selected anterior to posterior ROIs (located between ROIs 3 and 4) and emerged due to stronger activation to letter strings compared to FF in controls and an opposing trend in dyslexics. The right vOT cluster, however, was located more laterally than the ROIs and reflects stronger activation to FF compared to letter strings in dyslexics (see 4.4.4 Post-hoc Regions of Interest, p. 28, for ROI analyses on these interaction regions).

Further whole brain analyses on group differences to each individual stimulus condition and the main effect of group are listed in Table 4.7 on page 50 (also see Figure 4.6 of supplemental material, p. 44).

4.4.3 Occipitotemporal Regions of Interest

Compared to rest, percent signal change was generally strongest for FF in the right hemisphere (hemisphere x type, $F(3,99) = 59.39$; $P < 0.001$). In the left hemisphere, FF signals of controls but not dyslexics were lower than letter string signals (hemisphere x type x group, $F(3,99) = 11.65$; $P < 0.001$). This interaction pattern mainly resulted from the three most anterior ROIs (hemisphere x type x ROI x group, $F(15,495) = 2.59$; $P < 0.05$). For a complete listing of the effects of the four-way ANOVA see Table 4.2.

Table 4.2 Significant results of the four-way ANOVA in left and right occipitotemporal regions of interest

	F	*P*-value
ROI	$F(5,165) = 6.19$	$P < 0.01$
type	$F(3,99) = 8.74$	$P < 0.001$
hemisphere and ROI	$F(5,165) = 4.15$	$P < 0.05$
hemisphere and type	$F(3,99) = 59.39$	$P < 0.001$
ROI and type	$F(15,495) = 9.86$	$P < 0.001$
hemisphere, type and group	$F(3,99) = 11.65$	$P < 0.001$
ROI, type and group	$F(15,495) = 2.23$	$P < 0.05$
hemisphere, ROI and type	$F(15,495) = 9.33$	$P < 0.001$
hemisphere, ROI, type and group	$F(15,495) = 2.59$	$P < 0.05$

ROI = region of interest.

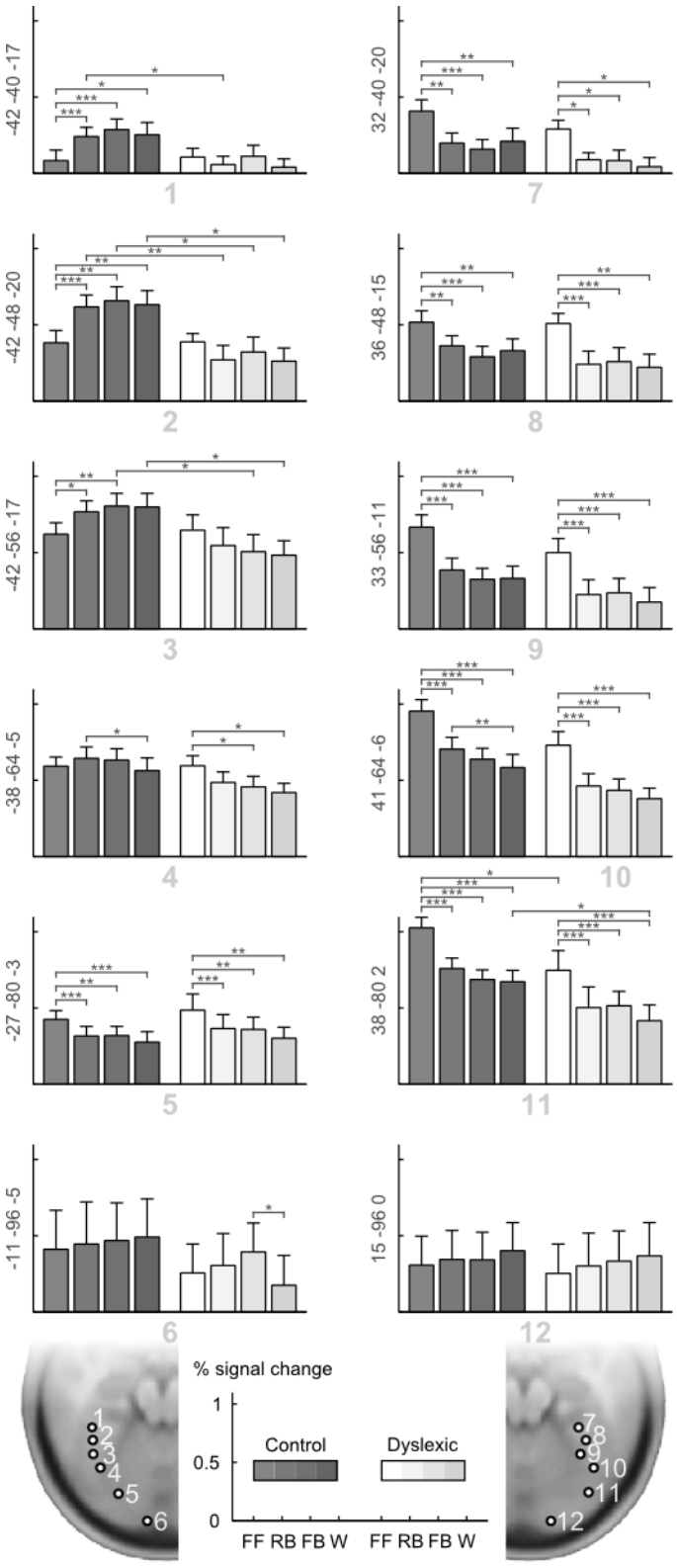


Figure 4.3 Percent signal change in 6 regions along the anterior to posterior axis of left and right occipitotemporal cortices (left and right panel, respectively). MNI coordinates are indicated at the y-axis and illustrated in section views at the bottom. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, error bars represent 1 SEM. Abbreviations: FF = false fonts, RB = rare bigrams, FB = frequent bigrams, W = words.

Separate repeated measures ANOVAs for the left and right hemispheres were also computed. The left hemisphere showed the expected interaction of ROI, type and group ($F(15,495) = 3.80$; $P < 0.001$), whereas the right hemisphere did not ($P \approx 0.74$).

The bar plots (Figure 4.3) confirm that there is stronger activation for letter stimuli compared to FF at the three most anterior left ROIs of controls, whereas there are no differences in dyslexics. In controls, these ROIs showed linear effects if tested across all conditions (all $P < 0.01$) but not if tested across only the three letter string conditions (all $P > 0.4$). A quadratic function best described the pattern across all conditions ($P < 0.001$ / 0.001 / 0.01 at Y = -40 / -48 / -56, respectively). Dyslexic's patterns were neither explained by linear nor quadratic functions. Accordingly, these left anterior ROIs showed no significant differences between any of the three types of letter strings in neither group. Furthermore, these ROIs showed stronger activation in controls compared to dyslexics for some letter string types but never for FF. Importantly, dyslexics also failed to show letter specificity in any vOT region if group-tailored ROIs (see 4.3.4 fMRI Acquisition and Analysis, p. 22) were used.

ROI 5 (Y = -80) exhibited a very reliable preference for FF stimuli compared to letter strings in both groups. Most likely, this region reflects activation patterns of lingual gyri (Figure 4.4) due to their close proximity, and it is not part of a posterior to anterior fusiform gradient of increasing print specificity, if existent.

Recalculation of these ROI analyses was also done with stimulus repetition as first level parametric modulator, leading to the same results. Recalculation with less smoothed data (3 mm FWHM) was also done. All critical results reported above remained significant, although at slightly lower levels in some cases.

4.4.4 Post-hoc Regions of Interest

Further ROI analyses were mainly based on significant group by condition interaction clusters that indicated condition-specific aberrances in dyslexia (Figure 4.4). Generally, the majority of significant differences was found between FF and letter strings, irrespective of the exact type of letter string. Lower FF than letter string activity was observed in left MTGp, left STGp, left IPL, and left middle vOT regions of controls but not dyslexics. Higher FF than letter string activity was observed in right lateral vOT and cerebellar Crus I regions of only dyslexics, as well as in left and right lingual gyri of both groups. In controls, posterior temporal regions and IPL exhibited staircase shaped patterns of gradual activation increase with growing word-likeness. Linear effects were highly significant for STGp and MTGp (both $P < 0.001$) across all four conditions and remained significant if tested without the FF condi-

tion ($P < 0.001$ and $P < 0.1$, respectively). In dyslexics, there was a significant linear effect in the STGp ($P < 0.05$) if tested across all conditions but not if tested without FF.

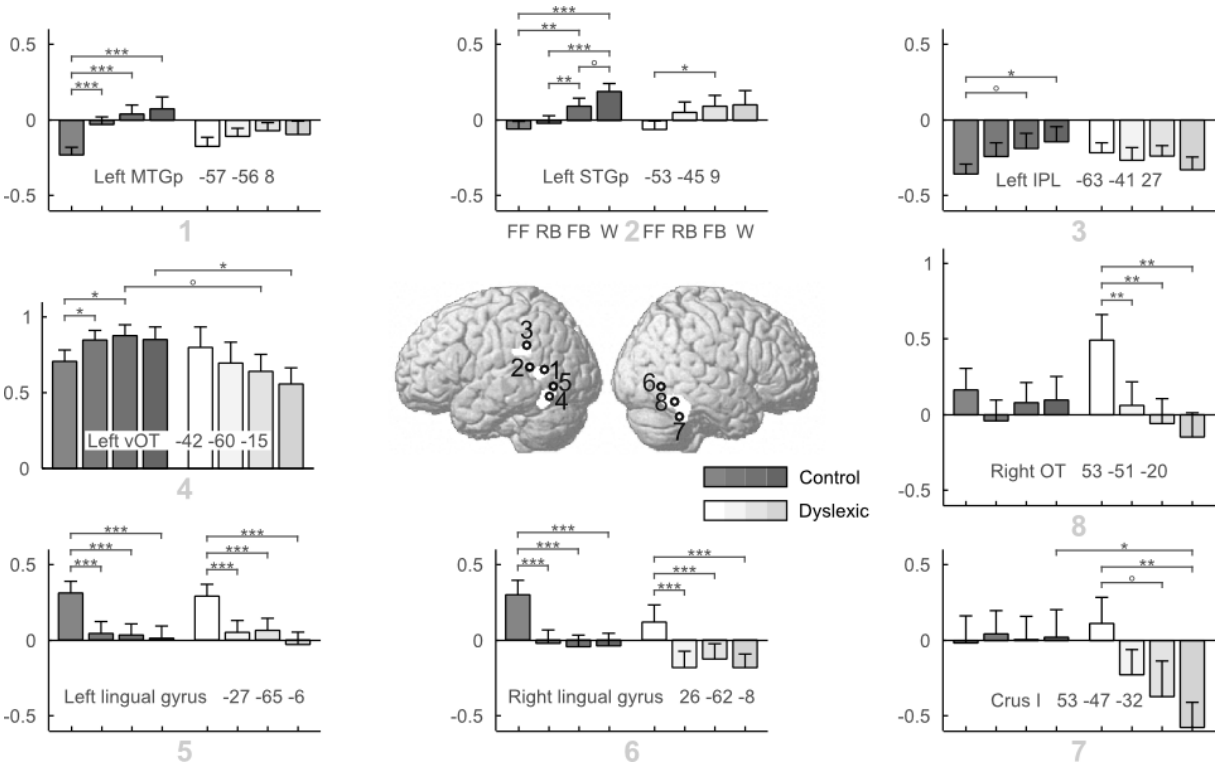


Figure 4.4 Percent signal change in further regions of interest, mainly based on the significant group by condition interaction (see bottom left image of Figure 4.2, p. 25). °$P < 0.1$, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, error bars represent 1 SEM, MNI coordinates. Abbreviations: FF = false fonts, RB = rare bigrams, FB = frequent bigrams, W = words, MTGp = posterior middle temporal gyrus, STGp = posterior superior temporal gyrus, IPL = inferior parietal lobule, vOT = ventral occipitotemporal.

4.4.5 Correlations Between ROIs and Reading Scores

Across the extended sample of 43 adolescents, correlations at a $P < 0.01$ threshold emerged between word or pseudoword reading scores and percent signal change in left and right hemisphere ROIs as listed in Table 4.3. All correlations were in the positive direction. Detailed scatter plots with correlation coefficients also for the dyslexic and the control group separately are provided in the supplemental material (Figure 4.7, p. 45). In all left hemispheric ROIs the correlations were driven by the control group and there was no significant positive correlation in the dyslexic group. In the right hemispheric ROI, however, correlations were more significant for the dyslexic group.

Table 4.3 Significant correlations at $P < 0.01$ between percent signal change in occipitotemporal regions of interest and current reading fluency

	Current reading fluency scores for	
	words	pseudowords
Left hemisphere		
ROI 1, for conditions:	FB	W, FB
ROI 2	W, FB, RB	W, FB, RB
ROI 3		W, FB
Right hemisphere		
ROI 11	W, FB, RB, FF	

FF = false fonts, RB = rare bigrams, FB = frequent bigrams, W = words, ROI = region of interest.

4.5 Discussion

The main aim of this study was to elucidate vOT differences between normal and impaired adolescent readers by probing rapid visual print processing under minimized phonological demands. We found clear aberrances in impaired readers' left vOT organization, suggesting deficits in print sensitivity at bottom-up processing stages. These findings and their significance will be discussed subsequently.

4.5.1 Lack of Print Tuning in Dyslexics

Whole brain analyses revealed a condition-specific group difference in middle portions of the left vOT cortex (peak at MNI -42, -60, -15). A closer inspection using ROIs anteriorly and posteriorly to this interaction cluster reliably indicated stronger letter stimuli than FF activation in controls but not dyslexics at the three anterior ROIs. The most posterior of these ROIs (MNI -42, -56, -17) is equivalent to the location of the VWFA (Cohen et al., 2000). Dyslexics' left anterior vOT portions apparently have failed to attune to letter stimuli in the course of learning to read. Moreover, direct group comparisons of signal changes compared to rest showed similar signal intensities for FF. Signal changes to letter stimuli, however, showed group differences. Controls exhibited stronger activation than dyslexics in at least one letter condition at all three anterior ROIs. In comparison with the meta-analysis of Richlan et al. (2011), our reading impaired adolescents thus tended to exhibit vOT aberrances distributed more like those in adults than children, suggesting that these aberrances fully evolve when

typical readers reach advanced reading and fluency levels. Importantly, this "mature" dysfunction pattern is reached already in adolescence at the end of compulsory schooling, i.e., at a critical developmental stage where fluency and automatization is still trained at a high level before literacy experiences diverge due to different professional tracks. Notably, there were no group differences at more posterior left vOT sites, limiting the possibility that left anterior vOT impairments are but a downstream consequence of more posterior occipital dysfunctions. Thus, in line with previous literature (Ben-Shachar et al., 2011; Brem et al., 2010) we suggest that during the normal acquisition of reading skills left anterior vOT regions are increasingly engaged in visual print processing, and that such engagement fails in DD (B. A. Shaywitz et al., 2002). This interpretation is corroborated by the correlations obtained between reading fluency and activity in anterior ROIs in our extended sample. More specifically, these correlations were mainly driven by the control group, given that there was no such relationship in the dyslexic group if analysed in isolation. This points to qualitative differences in vOT organization between groups rather than quantitative differences along a continuum.

A lack of specializations along the left vOT cortex in DD has previously been shown by van der Mark et al. (2009; also see Wimmer et al., 2010). These authors, however, made use of an explicit phonological task (phonological lexical decision) and found reduced specialization in dyslexia primarily for phonologically effortful conditions. This leads to the possibility that phonological deficits mediated dyslexic left vOT abnormalities. Our findings instead provide strong evidence for dyslexic deficits in coarse print sensitivity of bottom-up pathways. Coarse, because the lack of sensitivity occurred for all letter strings alike, irrespective of the bigram frequency, pronounceability, or lexicality of stimuli.

A short note on the possibility that presentation rate might have been too fast for proper vOT processing in dyslexic participants. Although stimulus duration was below the latency of an eye saccade in typical readers (at least 150 – 175 ms), Rayner (1998) concluded that typical readers most likely acquire the visual information necessary for reading during the first 50 to 70 ms of a fixation. Considering that the aim of the task was not to actually read the stimuli but to provoke bottom-up vOT activation, we believe that also dyslexics were sufficiently able to process stimuli up to a level that was desired by the task. This is reflected in their near ceiling level detection rate, even though they exhibited longer RTs than controls on average. Differences in RT may reflect more effortful task accomplishment due to lacking vOT specializations, but they might also be attributed to higher levels of arousal considering that dyslexic participants probably did not feel as comfortable as controls. They might also be accounted for by general theories of temporal or fast sequential processing deficits in dyslexia

(Farmer & Klein, 1995; Hari & Renvall, 2001; Tallal, 1980). There was no effect of stimulus type on RT, which makes it unlikely that the condition-specific group effects in left vOT regions might be explained by RT differences. Also note that the present analyses were conducted in a block-wise fashion, so that possible temporal differences in the hemodynamic response between groups, which also might account for differences in RT, would not be appropriate for explaining the pattern of vOT results.

A further condition-specific group difference emerged in a right hemisphere cluster, located in the vOT cortex just laterally of the fusiform gyrus (peak at MNI 53 -51 -20). Notably, this effect was driven by stronger FF than letter stimuli activation in dyslexics and no corresponding differences in controls. Decreases in right vOT and inferotemporal activity with age-related progress in reading proficiency have previously been reported by Turkeltaub et al. (2003). However, these authors reported right hemispheric decreases in word-specific activation (words compared to false fonts) with successful reading acquisition rather than augmented false font-specific activation in abnormal skill development. Nevertheless, in line with Turkeltaub et al. (2003) we suggest that reading problems might be associated with impaired disengagement from right vOT nonlexical recognition systems. Increased involvement of the right hemisphere in reading disability has repeatedly been reported for temporoparietal (Pugh et al., 2000; Simos, Breier, Fletcher, Bergman, & Papanicolaou, 2000; Simos, Breier, Fletcher, Foorman, et al., 2000) and vOT regions (B. A. Shaywitz et al., 2002), and has sometimes been interpreted as a compensation for left hemispheric disruptions (Pugh et al., 2000, 2001; B. A. Shaywitz et al., 2002). The stronger correlations between right middle occipital activation and word reading fluency in dyslexic participants compared to controls could be interpreted in favour of a compensatory account (see supplemental Figure 4.7, p. 45). However, our finding of increased FF rather than print sensitivity at the anteriorly located interaction cluster does not point to an ancillary involvement of right hemispheric vOT areas. It rather supports notions of a failure to shift from right-hemisphere guided to left-hemisphere guided reading strategies (Bakker, 2006; Turkeltaub et al., 2003).

Inspection of right fusiform ROIs along the entire posterior to anterior axis showed heightened FF sensitivity for both controls and dyslexics alike in all ROIs except for the most posterior one that did not show any condition effects. Right fusiform preference is well documented for faces (e.g., Allison, Puce, & McCarthy, 2002) and objects (e.g., Szwed et al., 2011) compared to letter strings, and has also been reported for false font strings (Tagamets, Novick, Chalmers, & Friedman, 2000). The robust FF effect in both of our groups suggests

that dyslexics' organization within the right fusiform gyrus is intact with respect to our stimulus categories.

Taken together the impaired left hemisphere engagement in letter recognition and a nonimpaired FF sensitivity in the right hemisphere of adolescent dyslexics points to a specific deficit in developing an elaborate letter sensitivity within vOT regions, be it in the left hemisphere or, as compensation, in the right.

4.5.2 Altered Patterns in Temporal Gyri

In posterior middle (MTGp) and superior temporal gyri (STGp) of the left hemisphere controls showed a gradual activation increase with growing word-likeness, even if tested without FF. In dyslexics these gradual patterns were largely absent. MTGp activation has been associated with phonological code retrieval in word articulation and comprehension (Indefrey & Levelt, 2004) and, likewise, with lexical-semantic processing during implicit or explicit reading tasks (Friederici, Opitz, & von Cramon, 2000; Price, Moore, Humphreys, & Wise, 1997; Pugh et al., 1996; Simos et al., 2002). STGp activation has consistently been linked to phonological decoding and possibly also reflects phonological working memory or subvocal articulation (e.g., Buchsbaum & D'Esposito, 2008; Demonet, Thierry, & Cardebat, 2005; Price, 2000; Wise et al., 2001). It is also known as a site of AV integration (van Atteveldt, Formisano, Goebel, & Blomert, 2004; T. M. Wright, Pelphrey, Allison, McKeown, & McCarthy, 2003). In controls, the STGp most clearly exhibited a gradual pattern with least FF activation, most W activation, and gradual increments in between and therefore actually depicted the expected pattern for left anterior vOT regions. The lack of such a clear posterior temporal activation gradient in dyslexics supports theories of phonological deficits in dyslexia, and specifically suggests impairments in the automaticity of grapho-phonological conversion. Both MTGp and STGp have reliably been found underactivated in adult- but not childhood dyslexia (Richlan et al., 2009, 2011). Although speculative, posterior temporal markers of the well-documented phonological deficits might only become evident in comparison with sufficiently developed reading networks in later childhood and adolescence, in contrast to left precentral markers of impaired phonological processing that are evident already in childhood (Bach et al., 2010).

We cannot exclude that the phonological deficits observed here are a downstream consequence of impaired vOT orthographic processing, or, critically, vice versa. In an explicit reading task, activity has actually been found to more strongly modulate connectivity from posterior superior temporal regions to the vOT sulcus than vice versa (Richardson et al., 2011).

Although analysis of effective connectivity would also be needed here for definitive clarification, the present dissociation of a gradual activation pattern in controls' temporal regions and the lack of such a pattern in vOT regions calls into question that these patterns emerged primarily as a consequence of tight coupling. Such an interpretation supports the idea that the present rapid and implicit design might have reduced interactions between temporal and vOT regions. As mentioned in the introduction, there is evidence in the priming literature that the task context can have an influence on subconscious or automatic phonological and semantic processes (Nakamura et al., 2007; Norris & Kinoshita, 2008). Moreover, the effects of task become clearer if comparing the present posterior temporal patterns of control participants to Graves et al. (2010) who reported an increase in BOLD signal with decreasing bigram frequency within these regions during a word reading aloud task. In other words, the present passive viewing design reversed the activation pattern that has been found during an explicit task. Graves et al. (2010) interpreted that decreased bigram frequency results in increased efforts of grapho-phonological conversion and therefore leads to enhanced posterior temporal activation. With respect to the present task design, the most likely interpretation is that controls (and probably also dyslexics to some extent) exhibited automatic grapho-phonological conversion as a function of feasibility under time constraints (W > FB > RB; no conversion possible for FF). These diverging findings across studies point to differences in at least the engagement of deliberate higher-order reading related processes and they are in line with previous claims of strong task-related effects on neural activation patterns (Mano et al., 2012; van Atteveldt, Formisano, Goebel, & Blomert, 2007; Vinckier et al., 2007). Involuntary, task-unrelated phonological and semantic processes, on the other hand, might have been influenced by the present task context (Nakamura et al., 2007; Norris & Kinoshita, 2008), but their emergence can hardly be ruled out, given that they even occur in priming designs (Diaz & McCarthy, 2007; Kherif et al., 2011; Rastle & Brysbaert, 2006).

Taken together, we believe that the paradigm employed here and in Vinckier et al. (2007) is well suited for probing the bottom-up responsiveness of the vOT cortex in print processing, given that these regions are very reliably activated and that at least deliberate higher-order reading-related processes are well prevented. The posterior temporal aberrances in dyslexia suggest impairments in the automaticity of grapho-phonological conversion.

4.5.3 Altered Inferior Parietal Patterns

A further interaction of group and stimulus type emerged in the supramarginal gyrus of the IPL. Hoeft et al. (2007) have previously found reduced IPL activity and grey matter volume

in dyslexic adolescents. Similar to the STGp, the IPL appears to be involved in phonological operations and commonly exhibits increased activation during visual or auditory word processing (Jobard et al., 2003). We, however, observed consistent deactivation to all stimulus types against rest, which seems incompatible with phonological processing. Besides its role in the temporoparietal reading network (Pugh et al., 2001), the IPL is also considered a part of the brain's default network, which refers to a defined brain system that is preferentially active in a restful state while not focussing on the external environment (Buckner, Andrews-Hanna, & Schacter, 2008; Laird et al., 2009; Raichle et al., 2001). Notably, deactivation has been related to task difficulty (Lin, Hasson, Jovicich, & Robinson, 2011; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Pallesen, Brattico, Bailey, Korvenoja, & Gjedde, 2009; Singh & Fawcett, 2008) and also to increases in stimulus presentation rate (McKiernan et al., 2003; Rumsey et al., 1997). Therefore, controls might have detected targets with less effort in blocks of W compared to FF, whereas dyslexics might not.

A recent meta-analysis has speculated that bilateral IPLs are bimodal in nature: self-referential at rest (the default network mode) versus input driven and executive during external stimulation (Laird et al., 2009). In other words, the observed IPL responses might be a blend of two interacting modes: deactivation caused by task engagement and activation caused by phonological operations in response to external stimulation. Hence, less deactivation to W than FF might to some extent indeed reflect differences in phonological access. However, these accounts of the unexpected IPL findings are speculative and future investigations should carefully test the roles of endogenous and exogenous factors for default network dynamics. Taken together, we are unable to conclusively interpret the IPL interaction of group and stimulus type. But we agree with Richlan et al. (2011) that dyslexic abnormalities in task-positive activation have different implications than in task-negative activation.

4.5.4 Altered Cerebellar Patterns

Dyslexics also showed deactivations to letter strings in the superior semilunar lobule (Crus I) of the right cerebellum. Controls did not show any signal changes compared to rest. Crus I has indeed been associated with language processing (Stoodley & Schmahmann, 2009). Booth et al. (2007) modeled effective connectivity for this region and found that the strongest input unidirectionally arrived from the fusiform gyrus. They speculated that the cerebellum is either involved in relaying orthographic information to phonological brain regions or, alternatively, in amplifying and refining the input signal. The cerebellar deficit theory of dyslexia (Nicolson

et al., 2001) advocates cerebellar-vestibular aberrances that give rise to a series of higher-order impairments. Such aberrances have repeatedly been shown for gray matter density (Brambati et al., 2006; Brown et al., 2001; Eckert et al., 2005; Kronbichler et al., 2008; see Richlan, Kronbichler, & Wimmer, 2013, for a recent meta-analysis). Pernet et al. (2009) reported reduced gray matter volume of the right cerebellar declive as one of the most reliable markers of dyslexia. Functional imaging studies show less consistency (for meta-analyses, see Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008; Richlan et al., 2009). Our finding supports, although little conclusive, functional differences in superior cerebellar portions in dyslexia.

4.5.5 Coarse, Not Fine-Grained, Left Occipitotemporal Print Tuning

In order to properly interpret dyslexic deficits at anterior left vOT sites, the functional contributions of this region to print processing are highly relevant. Dehaene et al. (2005) conceptualized this region as a posterior to anterior system of increasing sensitivity to regularities in print. We therefore had hypothesized to replicate a fine-grained gradient of increasing word sensitivity in controls (Vinckier et al., 2007). Whereas there was a clear difference between letter strings and FF at anterior left vOT sites, the three letter string conditions evoked responses of comparable magnitude. This result remained if data were smoothed less or if data were processed exactly following Vinckier et al. (2007). Whereas the absent difference between FB and W might still be compatible with findings of Vinckier et al. (2007), the absence of a difference between RB and W (or RB and FB) is a discrepancy. Note that our stimulus material succeeded in evoking a gradual signal increase in controls' left superior temporal gyrus (STG), as discussed above.

An explanation for the discrepant finding might be differences in reading proficiency or age (adolescent in our group) between studies. Considering that highly proficient readers might exhibit more pronounced orthographic tuning, ROI analyses were repeated in the subgroup scoring above the 80th percentile on word reading fluency (N = 12 adolescents whose mean reading score also exceeded the average of our adult Swiss norm group). This also did not reveal a fine-grained gradient. Moreover, investigations on age-related changes in left vOT regions do not support phases of congenital vOT maturation. Activity in left vOT regions to print either increases with emerging reading skills rather than age (Ben-Shachar et al., 2011; Brem et al., 2010; B. A. Shaywitz et al., 2004; B. A. Shaywitz et al., 2002; also see the present correlational results), decreases with age (Madden et al., 1996), or shows no differences in word specialization between adolescents and adults (Brem et al., 2009; Turkeltaub et

al., 2003). Hence, the discrepant vOT finding between studies remains unresolved. Possibly, a left vOT gradient is induced only if a high level of reading proficiency is upheld over several years through to adulthood, an assumption that we cannot test with adolescents. Differences in study designs may also have had an impact. In the present study stimuli were repeated eight times, whereas Vinckier et al. (2007) had no stimulus repetitions. However, the present findings remained unchanged after regressing out stimulus repetition (see 4.5.6 Limitations, p. 38). Moreover, other paradigm modifications (jittered versus constant SOA) as well as language differences might be an explanation (German with high spelling–sound consistency versus French with less consistency, compare Paulesu et al., 2001).

An alternative "interactive account" of the left vOT cortex (Price & Devlin, 2011) questions the notion of increasingly selective print tuning. Instead it suggests that this region serves as an interface for the integration of visual feedforward (e.g., orthographic) and top-down (phonological and semantic) activations. Integration is assumed to be absent in pre-literates, effortful during learning to read, and efficient in expert readers. These three developmental stages are reflected in an inverted u-shape of activation levels in left vOT regions with low, high, and medium activity during print processing, respectively. This account therefore provides a compatible framework to support the afore-mentioned notion that real reading expertise might only emerge after several years of proficiency – a possible explanation for differences between the present findings and those of Vinckier et al. (2007). This account also acknowledges modulations of vOT responses by task demands. For instance, Mano et al. (2012) had their participants focus on either linguistic (overt stimulus naming) or nonlinguistic (brightness judgement) aspects of stimuli. Notably, they found that left vOT responses were stronger for words and pseudowords compared to consonant strings during linguistic but not during nonlinguistic processing. The present task was devised as nonlinguistic in nature and our results indirectly support task-related modulations. We argue that the absence of differential vOT responses to the three types of letter strings is a consequence of the bottom-up nature of the task. The reliable underactivation to FF in controls therefore suggests that left vOT regions are coarsely tuned in a bottom-up fashion, possibly at the level of individual letters (Baker et al., 2007; Xue & Poldrack, 2007). Importantly, the interactive account does not deny that "visual experience results in plastic changes that tune the receptive fields to facilitate recognition of the most commonly occurring patterns" (Price & Devlin, 2011, p. 249). Our findings therefore seem more compatible with the interactive than the gradient account.

With respect to dyslexia, these results point to a deficit in coarse rather than fine-grained print tuning, as already mentioned. Coarse tuning deficits have previously been reported for dyslex-

ic children in the initial phase of learning to read, based on absent differences in electrophysiological responses to words versus symbol strings (Maurer et al., 2007). Previous studies on dyslexia that, unlike Maurer et al. (2007) and the present one, made use of an explicit reading task and that found left vOT activation differences to various types of letter strings in controls have interpreted lacking vOT specialization in dyslexic participants rather as a tuning deficit at the sublexical or lexical level (Richlan et al., 2010; van der Mark et al., 2009; Wimmer et al., 2010), given that prominent accounts on left vOT functionality do not explicitly refer to the letter level but rather to (sub)lexical levels (Binder et al., 2006; Dehaene et al., 2005; Kronbichler et al., 2007; Kronbichler et al., 2004; Vinckier et al., 2007; but see Baker et al., 2007; Xue & Poldrack, 2007). However, the possibility that dysfunctions are critical already at the letter level has recently been acknowledged in a meta-analysis (Richlan et al., 2011). Again, we argue that the previously observed presence of differential left vOT responses to different types of letter strings in fluent readers might be a confound of interacting higher-order effects on the vOT cortex due to explicit reading tasks.

It is therefore critical to design tasks that specifically isolate vOT deficits and our study reflects a first attempt in doing so. Our findings therefore substantially add to previous findings of dyslexic vOT deficits, because phonological confounds may largely be ruled out.

From an aetiological perspective, it has repeatedly been suggested that vOT print tuning develops by means of higher-order guidance of phonological temporal brain regions and that phonological deficits might thus cause vOT impairments (Brem et al., 2010; McCandliss & Noble, 2003; Sandak et al., 2004; Share, 1995; Spironelli et al., 2010). As a consequence, vOT deficits most likely become a proximate neural marker for impairments in proficient reading, as implied by previous and our observations of correlations between reading fluency and left vOT print sensitivity, as well as by studies on alexia (see 4.2 Introduction, p. 16). Phonological deficits, on the other hand, might play a more primordial role in the aetiology of DD.

4.5.6 Limitations

Each stimulus was repeated eight times (or seven, if replaced by a target). This repetition may have led to priming or familiarity effects interacting with the stimulus conditions. Left vOT activation has previously been found to decrease with repetition during an explicit reading task in typical readers (Pugh et al., 2008). Poor readers showed a similar decrease for a few repetitions but a reliable increase after three to six repetitions (Pugh et al., 2008), which suggests that group differences might fade after many repetitions. In order to rule out this possi-

bility as well as the possibility that our findings are driven by other unintended priming effects, we repeated all analyses with repetition as a first level parametric modulator. This did not change the above reported pattern of significances in any region (vOT, STGp, MTGp, etc.) although an interaction of repetition (as parametric modulator) and stimulus type emerged in bilateral STG, as well as the left anterior cingulate and attached extra-nuclear tissue, the left precuneus, and the right postcentral gyrus (see supplemental Figure 4.8, p. 46). Importantly, this interaction was not further modulated by group. The lack of repetition and group by repetition effects in vOT regions, which is in contrast to Pugh et al. (2008), might be another consequence of the bottom-up nature of our task, although this remains speculative.

A second limitation relates to automatic phonological activation, which apparently occurred in controls and possibly also to a smaller extent in dyslexics. Future investigations that specifically target bottom-up processing in dyslexia might attempt to further reduce task-unrelated automatic processes. However, given that reading is an inherently interactive process (Price & Devlin, 2011) it is questionable whether such designs may be achieved without departing too far from mechanisms essentially involved in reading.

4.6 Conclusion

The present findings provide strong evidence that dyslexic left vOT pathways lack print specialization during rapid bottom-up stimulation under minimized phonological or semantic task demands. If reading skills develop insufficiently, such pathways apparently fail to properly attune to basic elements (e.g., Latin letters) of the respective writing system and can be probed independently of phonology. To the best of our knowledge, dyslexic vOT aberrances have not been probed under similar conditions before, especially not in adolescents.

4.7 Acknowledgements

This research was supported by the Swiss National Science Foundation [grant number 32_125407]. We are grateful to our participants and their families. We also thank the physics and radiology teams of Children's Hospital Zurich for their kind assistance, as well as Martina Liechti for assistance with data recordings. We would also like to thank the anonymous reviewers for their helpful comments.

4.8 Supplementary Material

4.8.1 Construction of Letter Strings

The primary construction criterion was to achieve homogeneous levels of aggregated bigram frequency within each set of letter strings (i.e., conditions RB, FB, W), and to maximize differences between RB vs. FB and RB vs. W while minimizing differences between FB vs. W. Letter strings were generated by the WordGen application (Duyck, Desmet, Verbeke, & Brysbaert, 2004) and bigram frequency was assessed by comparing the stimuli to the integrated CELEX Lexical Database (Baayen, Piepenbrock, & van Rijn, 1993). The letter stimuli were matched for stimulus length (5 characters, like the FF strings), relative occurrence of characters overall, and relative occurrence of beginning and ending characters, for instance each 40 item list started three times with the letter "M" and ended eight times with an "e". The three middle letters were shuffled without constraints.

Another criterion for the creation of stimulus sets was that stimuli may sequentially be presented with minimized character repetitions in consecutive strings and no character repetitions at the same position in consecutive strings. This was in order to optimize stimuli for a rapid serial design, where participants are not irritated by differences in word length and where habituation to stimuli is minimized by ensuring letter changes from each stimulus to the next.

4.8.2 EEG Acquisition and Analysis

The EEG was recorded inside of the scanner using MR-compatible caps (EASYCAP GmbH, Germany) with 64 Ag/AgCl electrodes. Electrode positions were according to the international 10-20 system with additional electrodes at AF1/2, AFz, C1/2/5/6, CP1/2/3/4/5/6, CPz, F5/6, FC1/2/3/4/5/6, FCz, FPz, FT7/8/9/10, Iz, Oz, P5/6, PO1/2/7/8/9/10, POz, TP7/8/9/10). O1/2 and FP1/2 were placed 2 cm laterally from the standard positions for more even coverage. Fz served as recording reference, AFz as ground. Electrooculogram (EOG) was recorded by two electrodes placed below the outer canthus of each eye. Electrocardiogram (ECG) was derived by attaching further electrodes to the right of the sternum and on the left chest underneath the heart. Safety resistors of 5 kΩ or 15 kΩ are integrated in scalp or EOG / ECG electrodes, respectively. Total electrode impedances were kept below 25 kΩ or 35 kΩ, respectively. Total impedances of reference and ground electrodes were kept below 10 kΩ. The EEG was moni-

tored and checked for quality during scanning via online correction software (RecView, Brain Products GmbH, Germany).

Signals were digitized with two 32-channel amplifiers (BrainAmps MR, Brain Products GmbH, Germany) at a sampling rate of 5 kHz (bandwidth 0.1 – 250 Hz, input dynamic range ±16.38 mV).

Offline data processing included correction of MR gradient and cardioballistic artefacts according to Allen et al. (2000). Data were bandpass filtered (0.3 – 30 Hz), downsampled to 256 Hz, and ECG channels were discarded. Residual artefacts including eye-movements were corrected by means of independent component analysis (e.g., Jung, Makeig, Humphries, et al., 2000; Jung, Makeig, Westerfield, et al., 2000; Srivastava, Crottaz-Herbette, Lau, Glover, & Menon, 2005). The EEG was then re-referenced to the average of all scalp and EOG channels (Lehmann & Skrandies, 1980). For ERP analyses, data were divided into epochs of 1125 ms including a 125 ms interval prior to the defined stimulus onset. To eliminate artefacts caused by extracerebral sources, epochs with a signal value exceeding ±100 μV in any channel were rejected. Epochs were then averaged for each subject according to the different stimulus categories. The obtained ERPs were segmented into 50 ms intervals such that P1 and N1 components were well covered. Topographical map series were then computed by temporally averaging over these 50 ms segments. In segments that primarily covered P1 and N1 latencies, the average of occipitotemporal channels PO7, PO9, O1 and PO8, PO10, O2 were used for left and right hemispheric mean amplitude quantization, respectively. These mean amplitudes were entered into a repeated measures ANOVA with hemisphere (left, right) and stimulus type (FF, RB, FB, W) as within-subject factors, and group (dyslexic, control) as between-subject factor.

4.8.3 Description of EEG Results

Computation of global field power (GFP) across all participants and conditions revealed two distinct ERP components. The first component, P1, peaked at around 120 ms, the second, N1, at around 205 ms. Potentially later components were, despite jittering, superimposed by subsequent P1 and N1 components and were therefore not further analysed. Figure 4.5A (p. 43) illustrates the segmented GFP and associated topographies for W and FF conditions of both groups.

Given that the N1 has repeatedly been associated with the earliest marker of print tuning in visual object processing (Allison et al., 1999; Bentin et al., 1999; Maurer, Brandeis, et al., 2005; Maurer, Brem, et al., 2005; Nobre et al., 1994; Tarkiainen et al., 1999), we compared

N1 mean amplitudes at left and right occipitotemporal channels (Figure 4.5B, p. 43). N1 responses in a segment from 188 to 238 ms were most pronounced for RB (main effect of type, $F(3,99) = 9.33$; $P < 0.001$). According to expectations, letter strings elicited stronger responses than FF in the left hemisphere but not in the right (type x hemisphere, $F(3,99) = 25.53$; $P < 0.001$). This interaction tended to be more robust in controls (group x type x hemisphere, $F(3,99) = 2.53$; $P < 0.1$). Interestingly, in dyslexics there was at least a trend in each type of letter string for left lateralized processing, whereas this was not the case in controls. There was no main effect of group, nor were there any differences in direct group comparisons.

For the P1 segment from 90 to 137 ms results were similar, except that there were no modulations by group. Again, RB evoked strongest responses (main effect of type, $F(3,99) = 13.40$; $P < 0.001$), and letter strings elicited stronger responses than FF in the left hemisphere and less so in the right (type x hemisphere, $F(3,99) = 8.31$; $P < 0.001$). P1 responses were generally right lateralized (main effect of hemisphere, $F(1,33) = 8.02$; $P < 0.01$).

4.8.4 Supplementary Figures

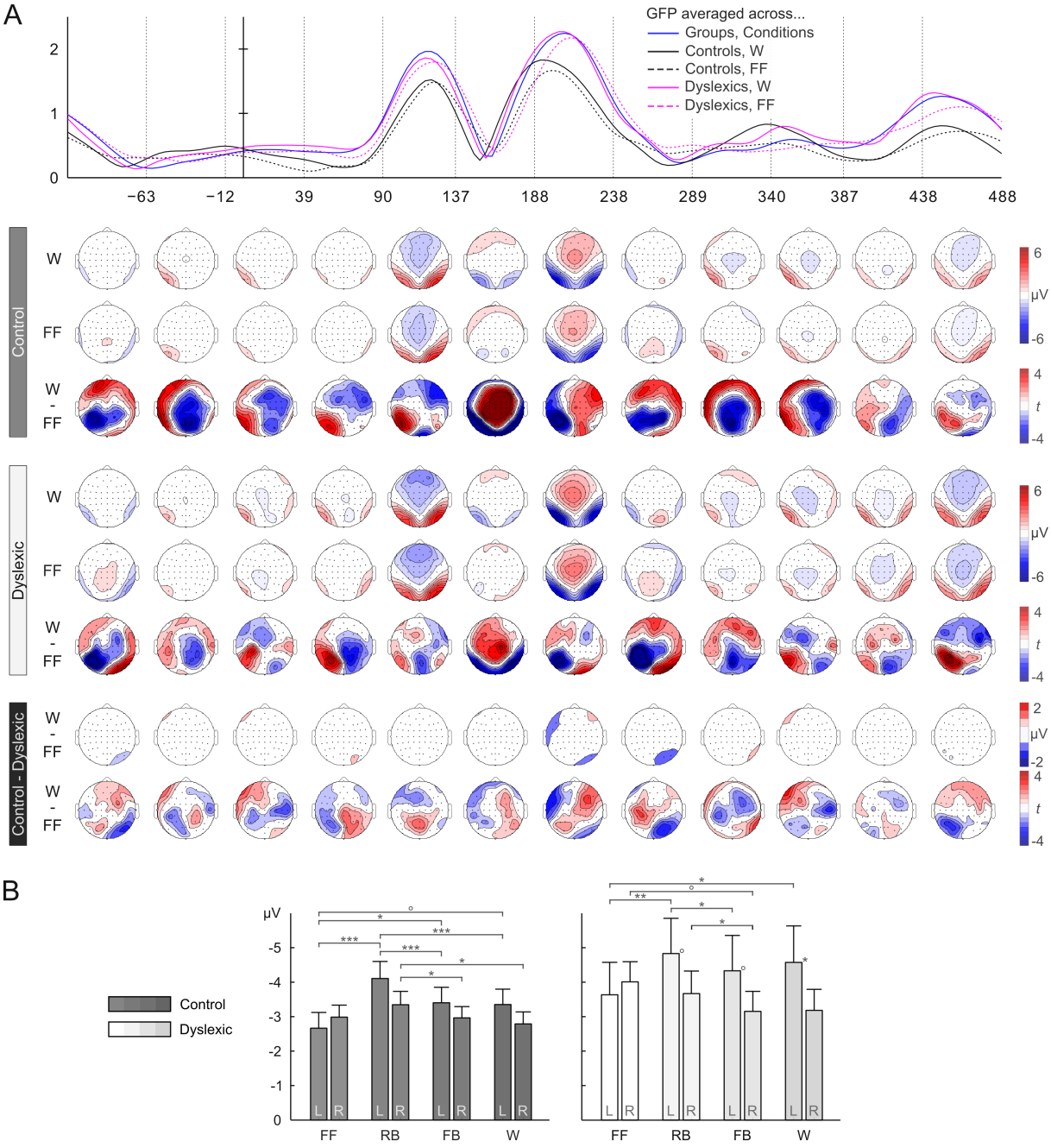
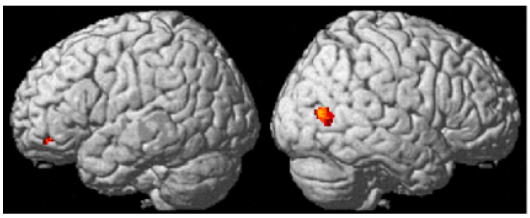
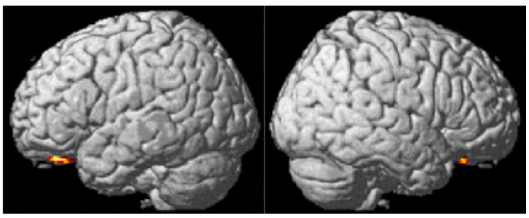


Figure 4.5 EEG Results. A) Overall global field power (GFP) time series, as well as GFPs for word (W) and false font (FF) stimuli for both groups. Corresponding mean voltage maps are depicted below for W and FF in controls (rows 1 – 2) and dyslexics (rows 4 – 5). *t*-difference maps show the W-FF contrast for controls and dyslexics (rows 3 and 6, respectively), as well as the group contrast for W-FF (row 8, also as voltage maps in row 7). P1 time window corresponds to 90 – 137 ms, N1 to 188 – 238 ms. B) Bar plots show occipitotemporal (average of PO7, PO9, O1 and PO8, PO10, O2 for left and right hemispheres, respectively) analyses for N1 mean amplitudes of all conditions and both groups. Error bars represent 1 SEM. Abbreviations: GFP = global field power, FF = false fonts, RB = rare bigrams, FB = frequent bigrams, W = words, L = left hemisphere, R = right hemisphere.

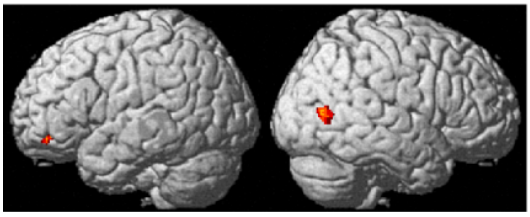
Main effect of group (4 stimulus types), Control > Dyslexic



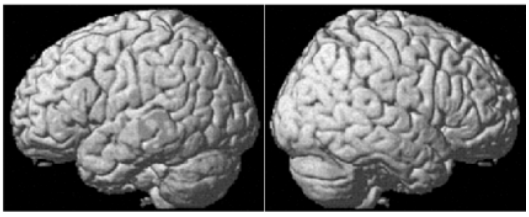
Main effect of group (4 stimulus types), Dyslexic > Control



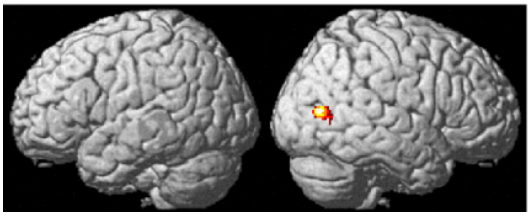
Group difference (3 letter string types), Control > Dyslexic



Group difference (3 letter string types), Dyslexic > Control



Group difference for FF, Control > Dyslexic



Group difference for FF, Dyslexic > Control

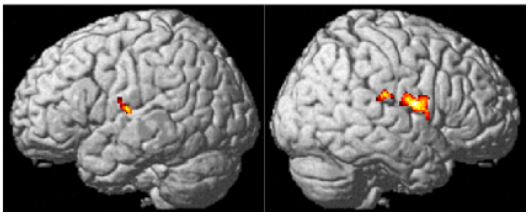


Figure 4.6 Selected fMRI activation for group differences. Brain renderings of differences for activations to all 4 stimulus types (top panel), to 3 letter string types (middle panel), and to FF (bottom panel) for controls minus dyslexics (left half) and dyslexics minus controls (right half). Threshold at $P < 0.005$ voxel-wise, cluster extent $k \geq 160$. Abbreviations: FF = false fonts.

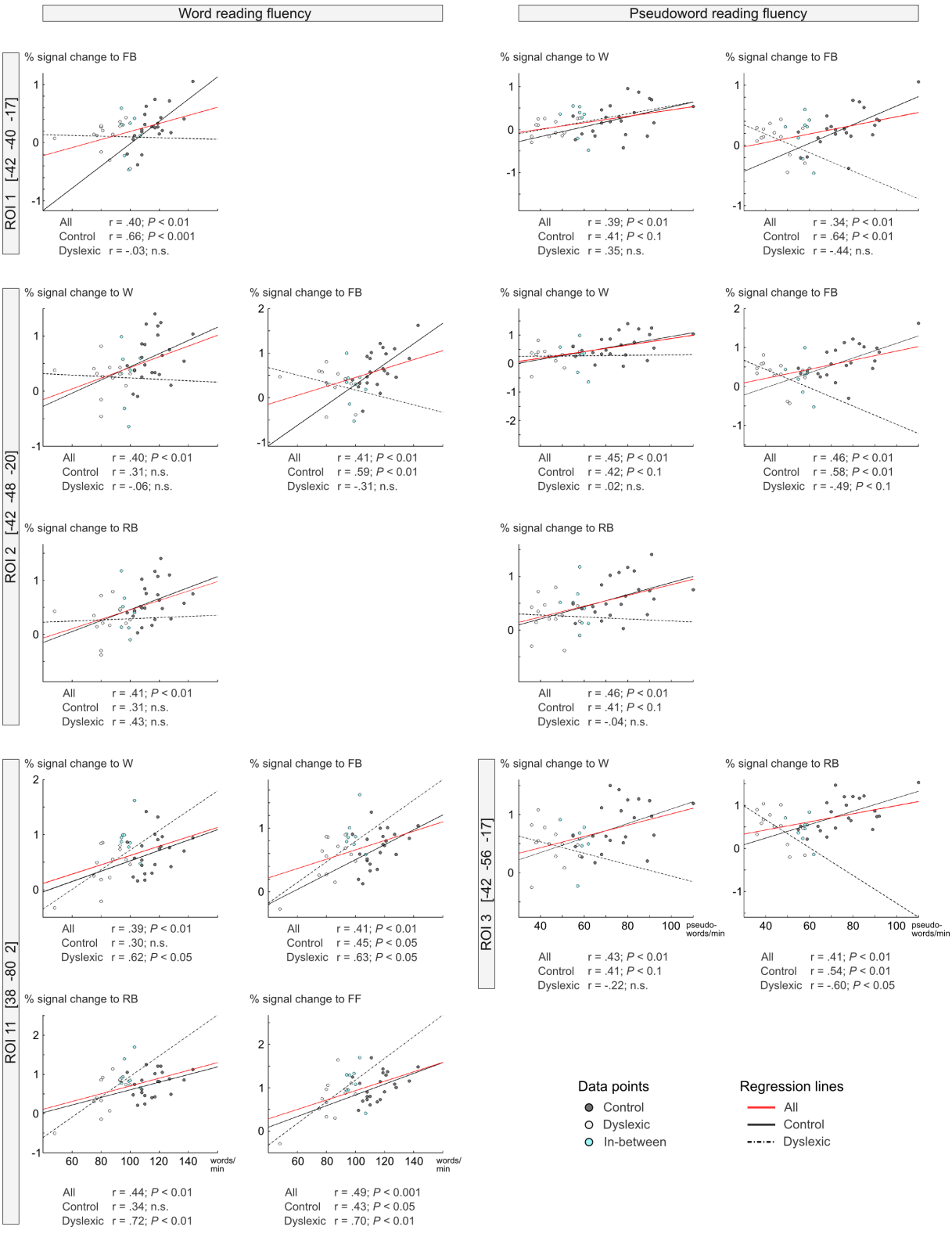


Figure 4.7 Significant correlations between percent signal change in occipitotemporal regions of interest and reading fluency measures. Scatter plots of significant correlations at $P < 0.01$ for the extended sample (N = 43) between percent signal change in ventral occipitotemporal ROIs and current reading fluency. ROI locations are indicated horizontally (also see Figure 4.3, p. 27). Reading fluency refers to correctly read items per minute, as shown along the x-axes of plots at the bottom. Red, black, and black dotted regression lines are based on the extended sample, the control sample, and the dyslexic sample, respectively. Corresponding correlation coefficients (Pearson's r) and *P*-values are listed underneath each scatter plot. Abbreviations: ROI = region of interest, W = words, FB = frequent bigrams, RB = rare bigrams, FF = false fonts, n.s. = not significant ($P > 0.1$).

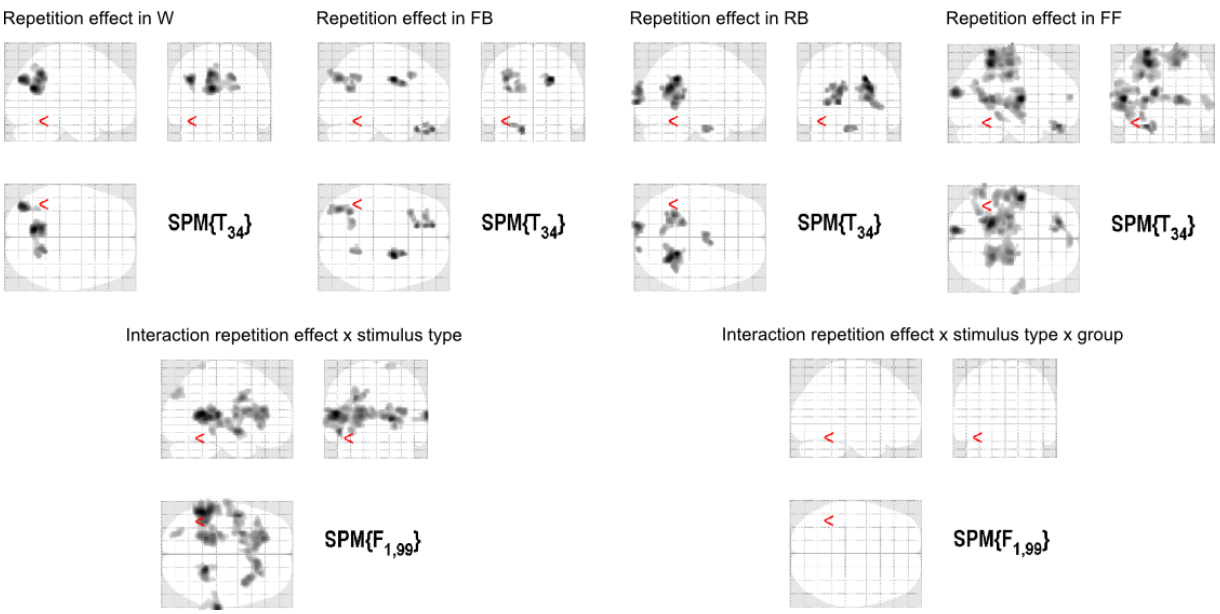


Figure 4.8 Effects of stimulus repetition as a parametric modulator. Glass brain views of the second level effects of stimulus repetition when entered as a parametric modulator at the first level. Top row: Effects of stimulus repetition in each of the 4 stimulus conditions across all participants; bottom row: Interactions of repetition effects, and stimulus type (left), as well as of repetition effects, stimulus type and group (right). The red arrow indicates the location of the Visual Word Form Area (MNI coordinates -42 -57 -20). Threshold at $P < 0.005$ voxelwise, cluster extent $k \geq 160$. Abbreviations: W = words, FB = frequent bi-grams, RB = rare bigrams, FF = false fonts.

4.8.5 Supplementary Tables

Table 4.4 Stimulus sets of all 4 conditions

W	FB	RB	FF
Stock	Scalg	Soecd	□∩∧ıΔШ
Honig	Jenok	Aadll	ΩΔrϽШ
Titel	Enage	Hoegn	□ſ◻□∧Ш
Monat	Katin	Snaes	ШıΔſϽШ
Trick	Itebe	Edild	Ш◻ſ◻ıШ
Klage	Akien	Weaee	ШΔ◻Δſ∏
Boden	Elost	Tnoag	⊓ӂΔıΔШ
Fauna	Wenfe	Hksro	ШıΔ∧λШ
Kraut	Adeid	Feetl	Ω◻◊ıϽШ
Atlas	Klige	Snawn	□ɪı∧rШ
Wiese	Bsera	Aglul	◊ΔıΔ◻Ш
Enkel	Talie	Tlaae	ШѡΔ∧Δ◻Ш
Junge	Zorar	Pimts	⊓∩\ſΔШ
Abend	Gelie	Ttnif	ΦΔϽ□◻Ш
Mango	Aselk	Bgdae	Γ□ɪıſ∏
Feder	Fdite	Lsaet	ΛΔ∧◻ıШ
Pfand	Soaun	Iaiir	Шſıφ◻Ш
Geist	Waner	Aeeee	Ω∧Ͻ\rШ
Anruf	Rogst	Wtgrr	ШΔ∩∧ıλШ
Wende	Hatan	Kltgt	<Δ□∩Δ◻Ш
Aroma	Atuer	Hnrog	ΨıɾΔıШ
Kunde	Penal	Zsfaa	ΦΔ◻ıΔШ
Start	Sdert	Mtsir	□ſ□□φ◻Ш
Allee	Hateo	Acltl	Γ□∩◻ıШ
Stern	Mdent	Giuek	⊓Δ◻ıΔШ
Radar	Hltig	Kdnbt	ΘıφΔ\Ш
Hotel	Lelos	Roeeo	◊◻◻ΔıШ
Staat	Trarl	Mlnae	[Δ□□φ◻Ш
Hafen	Stigo	Aeeet	ΔſϽıΔШ
Meile	Rlant	Srltn	Ш>ΛΔſ∏
Tango	Menwl	Fnuae	ΨıΔɾ◻Ш
Kreis	Alunf	Madrn	ΩΔ∧□ΔШ
Welle	Weaus	Knaet	⊓∧ɾΔɾШ
Lager	Koene	Rluae	ΔſΔ◻ıШ
Blatt	Terdt	Snnrt	⊓ıΛφΔШ
Insel	Baunl	Broee	□ΔſΔ□Ш
Rolle	Scgat	Woaia	Ψ□∧φıШ
Eisen	Flara	Kiulk	ΩΔſ◻ΔШ
Zweig	Kenfd	Eafnt	ΘΛφr□Ш
Salat	Mmane	Jlnee	⊓□□ſΔШ

Table 4.5 Activations of main conditions. Peak points (MNI coordinates and corresponding brain regions) within significantly activated clusters of each main condition against rest ($P < 0.05$, FWE) across 35 adolescents (control and dyslexic).

	MNI (x y z)	*Z*-score	Volume (mm³)
W > rest			
L Inferior / Middle Occipital Gyrus	-34 -87 -5	> 8	22160
R Lingual Gyrus / Sub-Gyral	26 -88 -6	7.49	15346
L Middle Frontal Gyrus	-57 2 51	5.34	304
R Inferior Frontal Gyrus / Precentral	41 3 33	4.80	41
L Superior / Inferior (Orbital Part) Frontal Gyrus	-33 48 -21	4.69	14
FB > rest			
L Inferior / Middle Occipital Gyrus	-34 -87 -5	> 8	25444
R Inferior Temporal Gyrus / Sub-Gyral	41 -64 -11	7.68	18448
L Middle Frontal Gyrus	-54 2 54	5.79	327
R Inferior Frontal Gyrus / Precentral	41 3 33	5.67	442
L Inferior Parietal Lobule / Precuneus	-28 -54 51	5.28	574
R Medial Frontal Gyrus / Paracentral Lobule	6 -25 62	5.22	155
RB > rest			
L Inferior / Middle Occipital Gyrus	-34 -87 -5	> 8	25630
R Fusiform Gyrus	27 -88 -6	7.75	19622
L Superior Parietal Lobule / Precuneus	-27 -54 50	5.26	432
R Inferior Frontal Gyrus / Precentral	41 2 33	5.11	209
R Superior Occipital Lobule / Precuneus	29 -67 33	4.92	125
R Superior / Middle (Orbital Part) Frontal Gyrus	23 50 -24	4.75	3
R Inferior Occipital / Lingual Gyrus	27 -105 -11	4.73	3
R Inferior Parietal Lobule	30 -54 47	4.71	7
FF > rest			
L Inferior / Middle Occipital Gyrus	-34 -87 -3	> 8	32596
R Inferior Temporal Gyrus / Sub-Gyral	42 -64 -11	> 8	30115
R Superior Parietal Lobule / Angular	30 -55 47	6.73	5788
R Inferior Frontal Gyrus / Precentral	42 6 32	6.05	1421
R Middle Frontal Gyrus / Precentral	45 0 50	5.13	179
R Insula	30 27 6	4.73	7

W = words, FB = frequent bigrams, RB = rare bigrams, FF = false fonts, L = left, R = right.

Table 4.6 Activations of Figure 4.2 (p. 25). Peak points (MNI coordinates and corresponding brain regions) within significantly activated clusters of the ANOVAs depicted in the Figure 4.2 ($P < 0.005$, $k \geq 160$).

	MNI (x y z)	*Z*-score	Volume (mm³)
Main effect of condition (4 stimulus types)			
Control			
R Inferior Temporal Gyrus	44 -66 -5	7.35	48232
L Middle / Superior Temporal Gyrus	-54 -52 9	5.87	21300
L Middle Occipital Gyrus	-31 -85 11	5.34	15704
L Precentral Gyrus	-55 -3 47	4.53	3021
R Supramarginal Gyrus	68 -48 32	4.36	4340
L Fusiform Gyrus	-42 -45 -20	4.20	2160
L Superior Occipital Gyrus / Cuneus	-10 -100 14	4.15	685
R Superior Occipital Gyrus / Cuneus	15 -93 18	3.97	2845
L Medial Frontal Gyrus / Supplemental Motor Area	-3 -1 62	3.71	992
R Superior Temporal Gyrus	62 -37 8	3.52	786
R Superior Parietal Lobule / Precuneus	24 -57 51	3.41	979
Dyslexic			
R Middle Occipital Gyrus	39 -79 9	5.71	57227
L Lingual Gyrus / Sub-Gyral	-27 -64 -6	4.54	18890
L Superior Parietal Lobule / Precuneus	-18 -76 45	3.26	3220
L Middle Temporal Gyrus	-54 0 -26	3.26	739
L Sub-Gyral	-31 -42 33	3.14	743
R Inferior Frontal Gyrus / Precentral	47 2 35	2.89	574
Main effect of condition (3 letter string types)			
Control			
L Middle / Superior Temporal Gyrus	-52 -45 9	4.02	4671
L Precentral Gyrus	-51 -3 45	3.54	1914
L Superior Frontal Gyrus / Supplemental Motor Area	-1 2 62	3.48	1137
Dyslexic			
L Superior Parietal Lobule / Precuneus	-18 -75 45	3.60	1873
R Middle Frontal Gyrus	42 12 57	3.28	543
R Superior Parietal Lobule	26 -61 56	3.16	2180
L Inferior Parietal Lobule	-34 -43 51	3.01	948
Group x condition (4 stimulus types)			
R Cerebellum Crus 1	53 -47 -32	3.72	3328
L Fusiform Gyrus	-42 -60 -15	3.41	1617
L Middle Temporal Gyrus	-57 -55 8	3.26	830
L Inferior Parietal Lobule / Supramarginal Gyrus	-63 -40 27	3.14	1175
R Precuneus	2 -82 42	3.11	1006
Group x condition (3 letter string types)			
R Precuneus	2 -67 50	3.18	1610

L = left, R = right.

Table 4.7 Further group differences. Peak points of group differences (MNI coordinates and corresponding brain regions) within significantly activated clusters of the main effect of group, the main effect across the three letter string conditions, and each individual stimulus condition ($P < 0.005$, $k \geq 160$).

	MNI (x y z)	*Z*-score	Volume (mm³)
Main effect of group (4 stimulus types)			
Control > Dyslexic			
L Inferior / Middle Frontal Gyrus / Rectus	-13 29 -17	3.26	948
R Sub-Gyral / Middle Temporal Gyrus	38 -64 3	3.10	975
Dyslexic > Control			
L/R Superior Frontal / Orbital Gyrus / Rectus	0 33 -26	3.69	651
R Sub-Gyral / Middle Temporal Gyrus	38 -64 3	3.10	975
Main effect of group (3 letter string types)			
Control > Dyslexic			
L Fusiform Gyrus	-34 -45 -14	3.39	847
L Inferior / Middle Frontal Gyrus / Rectus	-13 29 -17	3.24	1023
R Sub-Gyral	38 -64 3	3.09	840
Group difference for W			
Control > Dyslexic			
L Inferior / Middle Frontal Gyrus / Rectus	-25 42 -12	3.87	1711
R Middle Frontal Gyrus / Sub-Gyral	26 51 -14	3.31	746
R Sub-Gyral	39 -67 11	3.29	1262
L Fusiform / Parahippocampal Gyrus	-33 -45 -15	2.97	648
Group difference for FB			
Dyslexic > Control			
L Medial Frontal Gyrus	-7 65 15	3.61	699
R Insula / Heschl's Gyrus	38 -6 -2	3.58	2838
L Insula / Heschl's Gyrus	-37 -21 8	3.04	1323
Group difference for RB			
Control > Dyslexic			
L Fusiform Gyrus	-34 -45 -14	3.34	628
R Sub-Gyral	38 -63 3	3.16	746
Group difference for FF			
Control > Dyslexic			
R Sub-Gyral / Middle Occipital Gyrus	39 -72 9	3.10	854
Dyslexic > Control			
R Insula / Postcentral Gyrus	39 -12 5	4.22	6922
L Insula / Precentral Gyrus / Superior Temporal Gyrus	-37 -10 21	3.17	709

W = words, FB = frequent bigrams, RB = rare bigrams, FF = false fonts, L = left, R = right.

5 Study 2: The Level of Audiovisual Print–Speech Integration Deficits in Dyslexia

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5.1 Summary

The classical phonological deficit account of dyslexia is increasingly linked to impairments in grapho-phonological conversion, and to dysfunctions in superior temporal regions associated with audiovisual integration. The present study investigates mechanisms of audiovisual integration in typical and impaired readers at the critical developmental stage of adolescence.

Congruent and incongruent audiovisual as well as unimodal (visual only and auditory only) material was presented. Audiovisual presentations were single letters and three-letter (consonant-vowel-consonant) stimuli accompanied by matching or mismatching speech sounds. Three-letter stimuli exhibited fast phonetic transitions as in real-life language processing and reading. Congruency effects, i.e. different brain responses to congruent and incongruent stimuli were taken as an indicator of audiovisual integration at a phonetic level (grapho-phonological conversion). Comparisons of unimodal and audiovisual stimuli revealed basic, more sensory aspects of audiovisual integration. By means of these two criteria of audiovisual integration, the generalizability of audiovisual deficits in dyslexia was tested. Moreover, it was expected that the more naturalistic three-letter stimuli are superior to single letters in revealing group differences. Electrophysiological and hemodynamic (EEG and fMRI) data were acquired simultaneously in a simple target detection task. Applying the same statistical models to event-related EEG potentials and fMRI responses allowed comparing the effects detected by the two techniques at a descriptive level.

Group differences in congruency effects (congruent against incongruent) were observed in regions involved in grapho-phonological processing, including the left inferior frontal and angular gyri and the inferotemporal cortex. Importantly, such differences also emerged in superior temporal key regions. Three-letter stimuli revealed stronger group differences than single letters. No significant group differences in basic measures of audiovisual integration emerged. Convergence of hemodynamic and electrophysiological signals appeared to be limited and mainly occurred for highly significant and large effects in visual cortices.

The findings suggest efficient superior temporal tuning to audiovisual congruency in controls. In impaired readers, however, grapho-phonological conversion is effortful and inefficient, although basic audiovisual mechanisms seem intact. This unprecedented demonstration of audiovisual deficits in adolescent dyslexics provides critical evidence that the phonological deficit might be explained by impaired audiovisual integration at a phonetic level, especially for naturalistic and word-like stimulation.

5.2 *Introduction*

Developmental Dyslexia is a learning disability of neurobiological origin with substantial genetic risk (Pennington & Olson, 2008; Schulte-Körne et al. 2006). It is characterized by specific impairments in the acquisition of efficient reading and emerges despite normal intelligence, no obvious sensory deficits, and adequate instruction (Lyon et al. 2003; WHO, 1992). Dyslexia is one of the most widespread developmental disorders, affecting around 5% of school-aged children in German speaking countries (Schulte-Körne, 2010; Schulte-Körne & Remschmidt, 2003). The most commonly accepted cause of DD is thought to be a phonological processing deficit (Bradley & Bryant, 1978; Goswami, 2000; Ramus, 2003; Shaywitz & Shaywitz, 2005; Snowling, 2000; Tree, 2008; Vellutino et al. 2004). It has been suggested that this deficit is characterized by impairments in converting print (graphemes) into corresponding sounds (phonemes; Snowling, 1980). This hypothesis is appealing, considering that such conversions are obviously required in order to acquire efficient reading (Bradley & Bryant, 1983; Ehri, 2005). It also receives strong support from intervention studies in dyslexic or pre-school children that demonstrate improvements in reading skills through AV training programmes (Brem et al., 2010; Kujala et al., 2001; Lovio et al., 2012; Törmänen & Takala, 2009). Given the importance of AV conversion for reading, it is surprising that neurobiological origins of DD have until lately mainly been investigated by means of unimodal paradigms, both in the fMRI and EEG literature. Pekkola et al. (2006) were the first to use bimodal AV stimulations in order to probe phonological deficits in dyslexic adults. They found increased activation to incongruent stimulation in motor speech regions (Broca, left premotor cortex), which was more pronounced in dyslexic compared to typical adult readers. This was interpreted as increased use of subvocal motor-articulatory strategies during AV speech processing.

More recently, reduced congruency effects in impaired compared to nonimpaired readers were reported for superior temporal sulci (STS) and auditory cortices (planum temporale, PT; Blau et al., 2010; Blau et al., 2009). Specifically, stronger activation to congruent than incongruent letter–speech sound pairings was observed in these regions for typically reading children (Blau et al., 2010) and adults (Blau et al., 2009) but not for their dyslexic peers. STS regions have repeatedly been associated with multisensory integration and it has been argued that a distinction between congruent and incongruent pairings can only emerge after the unisensory inputs have been integrated successfully (Blomert, 2011; van Atteveldt, Formisano, Goebel et al., 2007). Thus, Blau et al. (2009, 2010) reasoned that letter–sound

integration is an emergent property of learning to read which develops inadequately in dyslexic readers, presumably as a result of lacking specialization at the neuroanatomical level. This has eventually been interpreted as a specific crossmodal binding deficit and as an impairment in the automated formation of unique grapho-phonological objects (Blomert, 2011). Note that Pekkola et al. (2006) had observed stronger activation to incongruent rather than congruent stimulation in the left STS of both groups. This difference to Blau et al. (2009, 2010) might be explained by attentional factors given that participants in Pekkola et al. (2006) but not in Blau et al. (2009, 2010) had to actively monitor congruency state (see van Atteveldt, Formisano, Goebel et al., 2007 for active versus passive processing). The significance of superior temporal regions for dyslexia is also supported by observations of reduced grey matter volume (Richlan et al., 2013; Welcome, Chiarello, Thompson, & Sowell, 2011).

According to a range of other criteria, the STS and adjacent gyral regions have repeatedly been related to multisensory integration: The "super-additivity" criterion, for instance, requires the response to crossmodally congruent stimuli to be stronger than the summed unisensory responses. In addition, the response to incongruent multisensory stimuli should be sub-additive compared to the summed unisensory stimulation, as has been shown for single cells of the superior colliculi in mammals (Kadunce, Vaughan, Wallace, Benedek, & Stein, 1997; B. E. Stein, 1998). These criteria are based on the general concept that sensory brain responses to stimulus elements that are processed independently should be additive. Accordingly, violations of additivity can indicate the presence of multisensory interactions, or of (non-additive) attentional or cognitive processes. Calvert et al. (2000) reported that BOLD signals in the ventral part of the human left STS also fulfilled both super- and sub-additivity criteria. Subsequent fMRI studies, however, could not replicate this rather strict conjunction of criteria (Hocking & Price, 2008, give an overview). Considering that the BOLD signal originates from large clusters of neurons containing not only multisensory integration cells, subsequent studies accepted more liberal criteria of AV integration for fMRI. van Atteveldt et al. (2004) found super-additivity (without corresponding sub-additivity) in bilateral PT and Heschl's sulci, but nowhere in the STS. However, the STS of both hemispheres showed stronger responses to congruent stimulation than to the maximum of the unisensory responses. This "response enhancement" (Beauchamp, 2005) was met in several studies (Beauchamp, Lee, Argall, & Martin, 2004; van Atteveldt, Formisano, Blomert, & Goebel, 2007). Electrophysiological studies have also made use of the super-additivity criterion and supported the role of the STS in AV integration (e.g., Besle, Fort, Delpuech, & Giard, 2004; Klucharev, Möttönen,

& Sams, 2003; Raij, Uutela, & Hari, 2000). Interestingly, all of these electrophysiological studies found sub- rather than super-additive effects for congruent AV stimulation.

In contrast to effects of congruency mode, criteria on the interplay of uni- and multimodal responses do not require grapho-phonological knowledge or conversion when probing AV integration. Comparisons of phonetically matching versus conflicting conditions therefore probe phonetic features of AV integration (Hocking & Price, 2008; Klucharev, et al., 2003; Ojanen, et al., 2005), whereas super-additivity effects probe general features of AV integration, including more basic and sensory aspects because phonological processing is no premise for the super-additivity criterion (e.g., Klucharev, et al., 2003).

As mentioned above, reduced congruency effects have been reported for dyslexia (Blau, et al., 2010; Blau, et al., 2009). However, criteria of super-additivity have never been tested in dyslexia, although they could clarify whether reading impairments originate from a more general AV deficit. The present study therefore includes both congruency as well as super-additivity approaches of testing AV integration. Because previous studies had found reduced AV integration in DD during passive (Blau, et al., 2010; Blau, et al., 2009) but not active congruency matching (Pekkola, et al., 2006), the design of Blau et al. (2010) was adopted to simulate AV integration during reading. Three further important aspects go beyond previous studies: First, by using consonant-vowel-consonant sequences (CVCs) in addition to single letter stimuli, we intended to go one step further towards realistic reading. CVCs are more speech-like than mere letters given their rapid acoustic changes (formant transitions) that are an immanent property of natural speech. A recent study used uni- and bimodal word and pseudoword stimuli and found reduced overall activation in the right STS of dyslexic adults, indicating less proficient engagement of circuits involved in AV processing (Kast, Bezzola, Jäncke, & Meyer, 2011). However, no contrasts to specifically test for AV integration were computed. The presently used CVCs were all without semantic content in order to avoid the engagement of confounding higher-order psycholinguistic processing. Of central interest was whether integrative effects behave differently in the CVC compared to the single letter condition. Second, participants were at an adolescent age by the end of compulsory schooling, i.e. at a critical developmental stage where reading proficiency is still trained at a high level before literacy experiences diverge due to different professional tracks. Audiovisual deficits have so far not been investigated in dyslexic adolescents. Third, EEG was recorded simultaneously with fMRI data in order to investigate temporal properties of AV integration and of group differences. Previous electrophysiological studies have confirmed AV integration deficits in dyslexic children (Froyen, et al., 2011; Widmann, et al., 2012) and adults (Mittag, et al., 2012).

Widmann et al. (2012), for instance, probed congruency effects in an oddball paradigm. Congruent symbol–sound pairings were interspersed with incongruent pairings. A component of the ERP that is associated with the orienting response to rare events was significantly less pronounced in dyslexic compared to control subjects. Considering the nonverbal stimulus material, the authors concluded that AV deficits could be more fundamental in nature, not restricted to impairments in grapho-phonological integration. The present study therefore aimed at clarifying the level of AV deficits by including and comparing the two approaches to test AV integration: super-additivity on the one hand and congruency effects on the other. Moreover, it was expected that CVC stimuli are more sensitive in revealing group differences due to their higher ecological validity with respect to reading.

5.3 Methods

5.3.1 Participants

A total of 45 adolescents was recruited by the end of 9th grade, the last grade of compulsory schooling in Switzerland (Table 5.1). All were part of a longitudinal sample either tracked since kindergarten (~75% of participants) or since 5th grade (Maurer et al., 2007; Maurer et al., 2003; Maurer et al., 2011; Schulz et al., 2008; Schulz et al., 2009). According to current and 5th grade reading scores, 22 adolescents were assigned to a nonimpaired reading group and 13 were categorized as reading-impaired. From the remaining 10 adolescents, 8 fell in between assignment criteria and were excluded. One subject (nonimpaired reader) was excluded due to excessive movement during recording (>2 mm), and one subject (dyslexic) due to ADHD comorbidity (see Kronschnabel, Schmid, Maurer, & Brandeis, 2013 for details on group assignment, exclusion criteria, as well as psychometric and reading scales). Participants reported normal or corrected-to-normal vision. All were native speakers of (Swiss-) German. Nonverbal IQ fell in the range of ± 1 SD, except in one control subject (nonverbal IQ = 75). Groups were matched in age, sex, handedness (Oldfield, 1971), nonverbal, and verbal IQ (Petermann & Petermann, 2007) as shown in Table 5.1.

Adolescents and their parents gave informed written consent upon participation. The study was approved by the local ethics committee.

Table 5.1 Demographic characteristics of control and dyslexic participants (number or M ± SD) and group differences (*t*-tests or Fisher's exact test)

	Control	Dyslexic	*P*-value
n	22	13	–
Age (years)	15.8 ± 0.3	16.1 ± 0.7	n.s.
Sex (male:female)	10:12	8:5	n.s.
Handedness (right:left:ambidextrous)	18:4:0	10:2:1	n.s.
Handedness continuous	57.6 ± 68.0	48.8 ± 61.4	n.s.
Estimated verbal IQ	112 ± 11	108 ± 17	n.s.
Estimated nonverbal IQ	110 ± 13	107 ± 11	n.s.
Estimated working memory	101 ± 13	85 ± 11	$P < 0.001$
Correctly read words/min			
currently (9^{th} grade)	115.4 ± 11.2	82.9 ± 13.1	$P < 0.001$
5^{th} grade	95.2 ± 13.7 (n=21)	49.1 ± 8.6 (n=12)	$P < 0.001$
Correctly read pseudowords/min			
currently (9^{th} grade)	76.1 ± 13.4	44.9 ± 7.5	$P < 0.001$
5^{th} grade	57.0 ± 9.7 (n=21)	30.3 ± 3.7 (n=12)	$P < 0.001$
Sentence processing speed	38.3 ± 7.4	25.8 ± 6.0	$P < 0.001$
Spelling errors	14.3 ± 9.7	38.4 ± 7.2	$P < 0.001$

M = mean, SD = standard deviation.

5.3.2 Stimuli and Task

The paradigm consisted of six experimental conditions: unimodal auditory CVCs, unimodal visual CVCs, bimodal (AV) congruent CVCs, bimodal incongruent CVCs, bimodal congruent letters, and bimodal incongruent letters. There were 15 different letters and 18 different CVCs. In all bimodal conditions the onset of both stimulus modalities was synchronous (see supplementary material on page 85 for further details).

All visual stimuli were presented for 600 ms in the centre of the field of view on a screen illuminated by a rear projector. They were in black lower case Arial font on white background. A cross hair appeared whenever there was no stimulus.

All sounds were digitally recorded (sampling rate 44.1 kHz) from a female native (Swiss) German speaker in a sound proof room. In the letter condition, the sounds formed isolated speech sounds (phonemes) rather than letter names. Acoustic stimulations were delivered in mono via MRI-compatible electrostatic headphones (Resonance Technology Inc., Northridge, California) during intervals free from scanner noise (see 5.3.4 fMRI Acquisition and Analysis, p. 58) and at a comfortable level.

The conditions were presented blockwise. Blocks consisted of three subunits that were separated by whole-brain fMRI scans. Each subunit comprised four stimulations of the same condition with a constant SOA of 950 ms (see supplementary Figure 5.4, p. 86, for an illustration). Successive stimuli within a subunit always differed. Each condition displayed 5 blocks (i.e., 5 x 3 subunits). The five blocks of each condition were evenly distributed during the course of the experiment, and two blocks of the same condition never appeared in succession. Blocks alternated with resting blocks. Resting blocks had a duration of either 2 or 3 subunits, alternating pseudorandomly. Overall, there were 54 stimulations per condition. Each visual and each auditory stimulus was presented equally often in each of the bimodal conditions as well as in the respective unimodal condition. Hence, over the course of the experiment congruent and incongruent bimodal conditions were matched for physical stimulus properties.
The task was a simple target detection that did not require active monitoring of congruency status. Targets existed in 3 versions: a C major triad piano sound, a visual "###" stimulus, or their AV combination. Each target version appeared twice per experimental condition, making it 6 targets per condition. Targets occurred at any position within a block. The main intention was to keep subjects alert and to avoid active monitoring of congruency mode.
The experiment took approximately 17 min. Subjects were familiarized with the task outside of the scanner und were instructed to fixate the cross hair at all times and to detect targets as quickly as possible.

5.3.3 Behavioural Data

A button press occurring between 100 ms and 2000 ms after target onset counted as a hit. Accuracy (hit rate) was compared between conditions and groups using Fisher's exact tests. Reaction time was analysed by a repeated measures ANOVA with the within-subject factor target type (unimodal auditory, unimodal visual, AV) and the between-subject factor group (dyslexic, control).

5.3.4 fMRI Acquisition and Analysis

MRI data was acquired on a 3.0 T (GE Healthcare) whole-body scanner. Due to the AV nature of the experiment, a clustered fMRI data acquisition sequence was used. Clustered sequences provide intervals free of scanning noise, which is convenient for acoustic stimulations (e.g., Bandettini, Jesmanowicz, Van Kylen, Birn, & Hyde, 1998; Blau et al., 2010; Edmister, Talavage, Ledden, & Weisskoff, 1999; Jäncke, Wüstenberg, Scheich, & Heinze,

2002; Shah et al., 2000). Based on pilot data and existing literature we opted for a time of repetition (TR) of 5900 ms and a time of acquisition (TA) of 1815 ms. Each subunit of a stimulus block was embedded in one TR and stimulations only occurred during the silent acquisition gaps. This way, 169 volumes with 33 axial slices covering the whole brain were acquired using a T2*-sensitive echo planar imaging (EPI) sequence (TA = 5.9 s; TR = 1.815 s; flip angle 75°; TE = 32 ms; FOV = 24 cm; matrix = 64 x 64; slice thickness = 3.3 mm; gap = 0.5 mm; in-plane resolution = 3.75 x 3.75 mm; SENSE factor = 2). The first scan was discarded due to scanner equilibration effects. A high-resolution T1-weighted anatomical image was acquired for each subject (SPGR sequence, 172 axial slices, slice thickness = 1 mm, in plane resolution = 1 x 1 mm, TR = 9.972 ms; flip angle 8°; TE = 2.912 ms; matrix = 256 x 204). Participants were provided with earplugs and headphones, and custom-made padding was used for head stabilization and further acoustic insulation.

Functional MRI data preprocessing and statistical analysis was done using SPM8 (Wellcome Trust Centre for Neuroimaging, London, http://www.fil.ion.ucl.ac.uk/spm/). Data were motion corrected and coregistered to the bias corrected anatomical scan. The DARTEL approach (Ashburner, 2007) was taken for normalizing and smoothing (8 mm FWHM) the data (according to SPM8 manual, Ashburner et al., 2010; also see Kronschnabel et al., 2013).

Statistical analysis of fMRI data was carried out in a two stage mixed effects model. At the subject level, stimuli of all conditions were modelled event-related using the standard SPM hemodynamic response function and its time derivative. Individual realignment parameters were entered into the regression model. Data were temporally high-pass filtered with a frequency cut-off period of 128 seconds, and serial correlations were accounted for using a first order autoregressive model.

At the group level, voxelwise whole brain random effects analyses and ROI analyses were conducted. To check whether brain responses were robust and sensitive to the task, all conditions were first contrasted against rest across all participants at $P < 0.05$, family-wise corrected for multiple comparisons (FWE). In order to probe AV integration, super-additivity contrasts involving uni- and bimodal CVC conditions and congruency contrasts involving only the bimodal conditions were computed. Specifically, super-additivity contrasts compared the activation of congruent CVC stimuli to the sum of unimodal auditory CVCs and unimodal visual CVCs [CVCcon > (CVCa + CVCv)] for the groups separately as well as the groups against one another. A mask of brain regions that responded significantly to each of the unisensory conditions (against baseline, $P < 0.05$, corrected for multiple comparisons using false discovery rate in order to reduce type II error) was applied to these contrasts.

Effects of congruency mode were obtained by computing whole brain contrasts involving the four bimodal AV stimuli as listed in Table 5.2. These contrasts are equivalent to a three-way repeated measures ANOVA with stimulus length and congruency mode as within-subject factors and group as between-subject factor. This way, all main effects and interactions of interest were tested.

All whole brain statistical mappings planned a priori and involving the factor group are depicted and reported at a $P < 0.005$ significance level, corrected for multiple comparisons using a cluster extent threshold ($k \geq 160$, equivalent to a volume of 540 mm^3, see Kronschnabel et al., 2013 for details).

Selected peak voxels were followed up by ROI analyses (spheres of 5 mm radius) to explore the pattern of percent signal change of all conditions at these sites. The mean percent signal change was derived from each ROI using MARSBAR on the smoothed data (http://marsbar.sourceforge.net, Brett et al., 2002). As described in the results section, ROI

Table 5.2 Stimulus length x congruency mode x group repeated measures ANOVA (bimodal conditions only)

1st level contrast	2nd level design	equivalent to
Mean of the 4 bimodal conditions	two-sample *t*-test (control vs. dyslexic)	ME group
SL – CVC	one-sample *t*-test (all participants)	ME stimulus length
	two-sample *t*-test	stimulus length x group
Congruent – incongruent	one-sample *t*-test	ME congruency mode
	two-sample *t*-test	congruency mode x group
(SL congruent – SL incongruent) – (CVC congruent – CVC incongruent)	one-sample *t*-test	stimulus length x congruency mode
	two-sample *t*-test	stimulus length x congruency mode x group

CVC = consonant-vowel-consonant stimuli, SL = single letter stimuli, ME = main effect.

values were in some cases re-entered into a repeated measures ANOVA in order to obtain further information about the constellation of effects and in order to obtain post-hoc *t*-tests (SPSS, Version 20.0, IBM Corp.). In these ANOVAs *P*-values were Greenhouse-Geisser corrected whenever sphericity assumptions were violated.

5.3.5 EEG Acquisition and Analysis

The EEG was recorded inside of the scanner using MR-compatible caps (EASYCAP GmbH, Germany) with 64 Ag/AgCl electrodes. Electrode Fz served as recording reference, AFz as ground. Details on electrode positions and impedances during measurements may be found in the supplementary material (see 5.8.1 Details on Stimulus Material, p. 85). Electrooculogram (EOG) and Electrocardiogram (ECG) were also recorded. The EEG was monitored and checked for quality during MRI scanning via online correction software (RecView, Brain Products GmbH, Germany).

Signals were digitized with two 32-channel amplifiers (BrainAmps MR, Brain Products GmbH, Germany) at a sampling rate of 5 kHz (bandwidth 0.1 – 250 Hz, input dynamic range ± 16.38 mV).

Offline data processing included correction of MR gradient and cardioballistic artefacts according to Allen et al. (2000). Data were bandpass filtered (0.3 – 30 Hz), downsampled to 256 Hz, and ECG channels were discarded. Residual artefacts including eye-movements were corrected by means of independent component analysis (e.g., Jung, Makeig, Humphries, et al., 2000; Jung, Makeig, Westerfield, et al., 2000; Srivastava et al., 2005). The EEG was then re-referenced to the average of all scalp and EOG channels (Lehmann & Skrandies, 1980). For ERP derivation, data were divided into epochs of 1125 ms including a 125 ms interval prior to stimulus onset. To eliminate artefacts caused by extracerebral sources, epochs with a signal value exceeding ±100 μV in any channel were rejected. Epochs were baseline removed (-125 to 0 ms) and averaged for each subject according to the different stimulus conditions. To check for basic activation patterns, the obtained ERPs were averaged across all participants and segmented into 50 ms intervals. Topographical map series were then computed by temporally averaging over these 50 ms segments.

EEG data were analysed analogous to fMRI data. RAGU, a randomization statistics toolbox for event-related scalp field data, was used to assess super-additivity and congruency effects (Koenig, Kottlow, Stein, & Melie-García, 2011). With respect to super-additivity, a repeated measures ANOVA with the within-subject factor modality (bimodal CVCcon, [unimodal CVCa + unimodal CVCv]) and group as between-subject factor was computed. The main effect of modality reflected whether super-additivity (or sub-additivity) was present across all subjects, and the interaction of modality and group reflected whether this effect was modulated by group. The main effect of group was of little interest for this analysis and is therefore not reported. With respect to effects of congruency mode, a repeated measures ANOVA was

conducted on the four bimodal conditions with stimulus length and congruency mode as within-subject factors and group as between-subject factor.

For both super-additivity and congruency effects, global field power (GFP) and topographic ANOVA (TANOVA) randomization statistics were computed in order to detect both global and regional effects. GFP, on the one hand, is a parametric assessment of map strength that is independent of topography. It equals the root mean square across all electrodes in the case of an average reference. TANOVAs, on the other hand, are an established method for comparing the topographical distribution of multichannel ERP data without the need for assumptions about the correlation structure among channels (Koenig & Melie-García, 2009; for similar approaches, see Greenblatt & Pflieger, 2004; Karniski, Blair, & Snider, 1994; Lobaugh, West, & McIntosh, 2001). The randomization statistics procedure is based upon the computation of residual topographies by comparing individual grand-mean topographies to grand-mean topographies across all conditions and / or groups (depending on the effect or interaction of interest). These residual topographies are used to create an effect size, which resembles the computation of the standard deviation. This effect size is tested against an effect size distribution obtained by randomization statistics, where group and / or condition assignments in each subject are randomly shuffled in order to obtain an estimation of the effect size under the null hypothesis (for details, see Koenig, et al., 2011, pp. 2-3; Koenig & Melie-García, 2009, pp. 176-178). All (T)ANOVAs were only computed for time points where topographies across all participants were consistent, that is, where a consistent relation between the event and particular brain electric fields existed (see Koenig & Melie-García, 2010). This procedure reduces false conclusions from inadequate time windows by identifying time points where signal noise predominates (see Koenig & Melie-García, 2010). Moreover, the super-additivity criterion was computed for only the first 350 ms after stimulus onset, because a valid application assumes that only sensory activities are included in the signals and no nonspecific activities that are common to unimodal and bimodal conditions and that are not integrated (e.g., attentive or motor processes). It is widely accepted that approximately the first 200 ms after stimulus onset are characterized by sensory-specific responses and that nonspecific components become more influential afterwards (Besle, et al., 2004; Giard & Peronnet, 1999; Hillyard, Teder-Salejarvi, & Münte, 1998). Early attentional effects have been found to influence responses mainly in a quantitative fashion (i.e., response enhancements; Clark & Hillyard, 1996; Correa, Lupianez, Madrid, & Tudela, 2006; Hillyard, et al., 1998), which is compatible with a valid application of the super-additivity criterion as long as quantitative modifications are similar across conditions.

To avoid false positives due to multiple testing, significant GFP and TANOVA effects had to persist for a minimum duration as quantified by RAGU. The algorithm computes how likely it is to obtain by chance continuous periods of significance for an equal or longer time than actually observed. This information of chance can be obtained via randomization statistics. Significant periods were further inspected by means of topographies (microvolt maps) and statistical maps (*t*-maps and maps with corresponding *P*-values).

5.4 Results

5.4.1 Behaviour

Target detection accuracy was not significantly affected by condition in neither group (both $P > 0.2$). Accuracy did not differ significantly between groups for any of the target types (unimodal auditory, unimodal visual, AV; all $P > 0.5$). Pooled across conditions, overall accuracy was 98.9% in nonimpaired and 98.5% in impaired readers.

Analysis of reaction times revealed a main effect of target type ($F(2,66) = 43.03$, $P < 0.001$) with no other effect becoming significant. Reaction times were shortest in the AV condition (M = 468 ms), and gradually increased over the visual (M = 524 ms) to the auditory condition (M = 578 ms, all $P < 0.001$). There was no significant group difference for any target type (all $P > 0.2$).

5.4.2 Neuroimaging

5.4.2.1 Basic Activation Patterns

fMRI

Basic activation patterns of each condition against baseline reflected typical auditory, visual, or combined processing. Across all adolescents, the unimodal auditory condition evoked greatest BOLD signals in bilateral STG, as well as in bilateral premotor regions. Unimodal visual CVCs most robustly activated inferior and middle parts of occipital lobes, premotor cortices, the superior parietal lobes of both hemispheres, and the left fusiform gyrus. The four bimodal AV conditions basically exhibited a combination of activation clusters found in the unimodal conditions. Details on these activation patterns may be found in the supplement (Table 5.4, p. 94, and Figure 5.5, p. 87).

EEG

The ERPs showed typical courses of deflections and topographies (see supplementary Figure 5.6, p. 88). Specifically, all conditions involving visual stimulation exhibited the typical P1 (80 – 150 ms) – N1 (150 – 270 ms) – P2 / P3 (ca. 270 – 550 ms) sequence within the first 500 ms after stimulus onset (Allison et al., 1999; Brandeis, Lehmann, Michel, & Mingrone, 1995; Brandeis, Vitacco, & Steinhausen, 1994; Brem et al., 2006; Maurer, Brandeis, et al., 2005; Maurer, Brem, et al., 2005; Maurer et al., 2006; Maurer et al., 2011). Around 700 ms a visual offset negativity started to emerge. This negativity reflects brain processes within the calcarine cortex associated with the offset of the visual stimulus (Huettel et al., 2004; Maurer, Brem, et al., 2005).

The unimodal auditory condition also exhibited topographies that were similar to previous reports on auditory processing of attended speech sounds (Froyen et al., 2011; Sheehan, McArthur, & Bishop, 2005). These include a frontocentral double-peaking positivity during the first 300 ms and a subsequent negativity at these sites, most likely reflecting superior temporal activity. During later segments (after 540 ms) an occipitotemporal positivity emerged, difficult to interpret given that previous evidence in such late segments is lacking.

5.4.2.2 Super-additivity Effects

fMRI

Testing for super-additivity [CVCcon > (CVCa + CVCv)] revealed no significant clusters in any group, even if lowering the significance level to $P < 0.05$. The inverse contrast (sub-additivity), however, revealed highly significant ($P < 0.05$, FWE corrected) clusters, mainly in superior parietal, middle to superior temporal, and precentral regions (see supplementary Table 5.5, p. 96). There were no group-specific differences in neither direction.

Given the absence of super-additivity effects, the super-additivity criterion was relaxed in a supplementary analysis such that the activation to congruent CVC stimuli was compared to the mean of the unisensory responses [CVCcon > ((CVCa + CVCv)/2)]. This relaxed criterion has been suggested in the case of fMRI (Beauchamp, 2005), but has also been criticized (Hocking & Price, 2008). Significant middle STG clusters were found in both groups (see supplementary Figure 5.7, p. 89, and Table 5.6, p. 96). However, as the corresponding ROI analyses show (Figure 5.7), responses to bimodal stimulation were not higher than the largest of the unisensory responses. Speaking of super-additivity thus seems inappropriate. More importantly, however, again no significant group differences were observed.

The absence of any group differences in super-additivity contrasts argues against a general or basic AV integration deficit in dyslexia.

EEG

Topographic consistency was fulfilled continuously after around 85 ms (see legend of Figure 5.1, p. 66) and repeated measures ANOVAs with factors modality mode and group were applied. Contrary to the concept of super-additivity, bimodal AV presentation elicited numerically lower GFP than the sum of unimodal presentations throughout the epoch (see main effect of modality in Figure 5.1). This difference became significant and passed the duration threshold after 234 ms. As topographies #3 and 4 show, there is a highly significant difference above left superior temporal electrodes (T7 / C5) that moves centrally around 300 ms. These are sub-additive effects (compare Figure 5.9 of supplementary material, p. 92). Given that the first 200 ms after stimulus onset are conceptually of most importance for super-additivity (see 5.3.5 EEG Acquisition and Analysis, p. 61), also significant periods within the P1 phase that did not pass the duration threshold were followed up by topography maps. In the period from 90 to 152 ms a (fronto-)central difference emerged (#1 and 2). From 105 to 121 ms a modality by group interaction was observed (#5), due to sub-additivity in dyslexics but not controls. This effect could either reflect group differences in AV integration, or it could reflect differences already in the involved uni- or bimodal conditions that propagate to the super-additivity contrast. As supplementary Figure 5.8 (p. 90, 90 to 137 ms latency) shows, there are very similar topographic group differences already in the (summed) unimodal conditions for this latency. This rather argues against group differences in AV integration.

Supplementary Figure 5.8 (p. 90) and Figure 5.9 (p. 92) also show the emergence of long lasting left occipitotemporal group differences in the super-additivity contrast. These emerged around 300 ms and lasted approximately until 800 ms post-stimulus. Inspection of the underlying conditions revealed that group differences once again were mainly driven by aberrant late responses to unimodal auditory and visual stimuli in dyslexic participants.

Hence, EEG data also did not support a general deficit in mechanisms of AV integration in dyslexia.

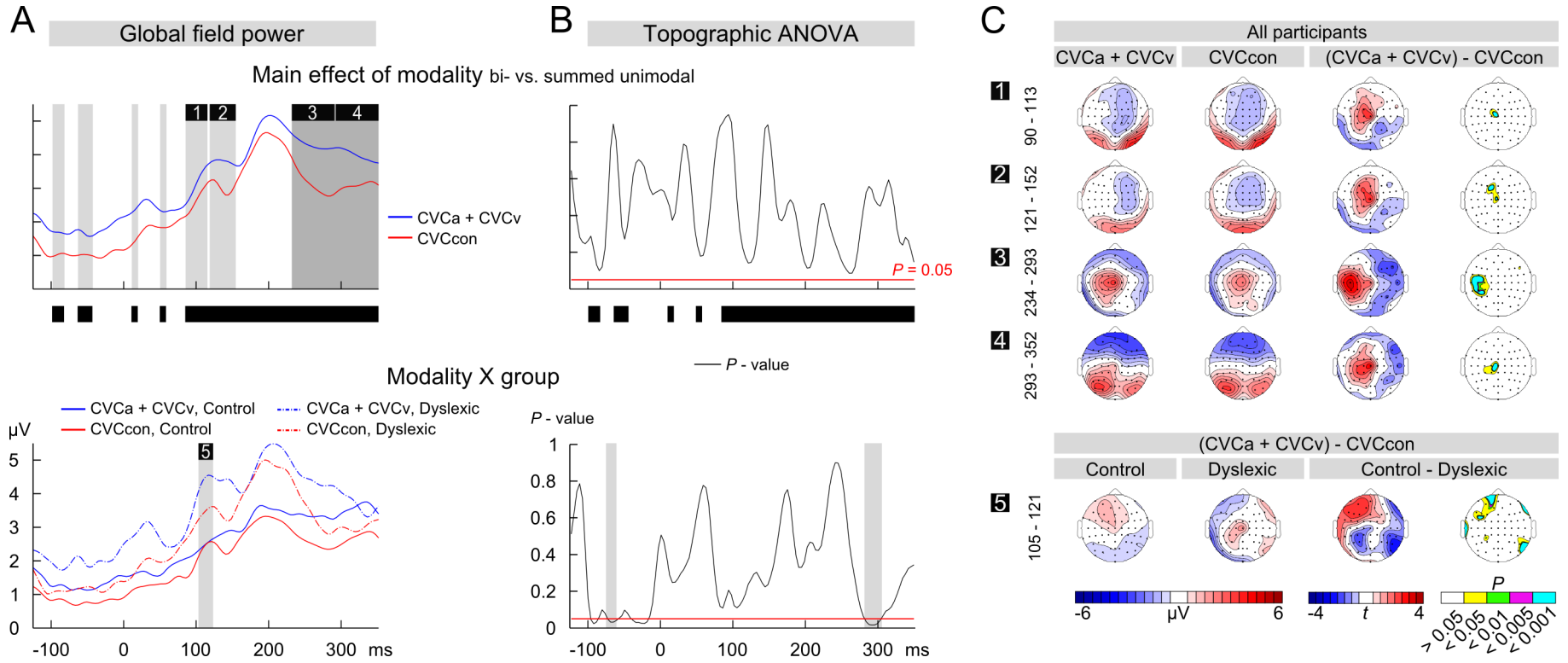


Figure 5.1 Results of global field power (A) and topographic ANOVA randomization statistics (B) of EEG data for the super-additivity criterion. Grey shading indicates significant time points ($P < 0.05$), dark grey shading indicates significance periods that also surpass adjustment for multiple comparisons (see 5.3.5 EEG Acquisition and Analysis, p. 61). The black bar below the uppermost graph indicates periods of significant topographic consistency across all 35 participants. Post-stimulus dark grey periods and significant P1 and N1 periods are illustrated by means of topographic displays (C). Voltage maps of the conditions that evoked significant GFP effects are depicted in two columns on the left, statistical comparisons (*t*- and *P*-maps) of these voltage maps are on the right. Time windows of these maps in milliseconds are indicated vertically on the left. Abbreviations: CVCa = unimodal auditory consonant-vowel-consonant stimuli, CVCv = unimodal visual consonant-vowel-consonant stimuli, CVCcon = congruent consonant-vowel-consonant stimuli.

5.4.2.3 Comparison of Congruent and Incongruent Conditions

fMRI

In order to investigate the effects of congruency mode, whole-brain analyses reflecting a three-way ANOVA with stimulus length and congruency mode as within-subject factors and group as between subject factor were conducted across the four AV conditions (see Table 5.2, p. 60). Figure 5.2 (p. 68) depicts rendered brain images of all main effects and interactions, Table 5.3 (p. 69) lists significant clusters. Group main effects across all bimodal conditions reflected stronger signals for dyslexics in bilateral frontopolar prefrontal cortices (Figure 5.2, p. 68, bar charts #1 & 2) and middle parts of the right cingulum. The main effect of stimulus length exhibited the strongest and most extended significance clusters of all effects. Large clusters with stronger activation to CVCs than single letters were located in bilateral lingual (#3) and superior temporal gyri. Single letters showed stronger signals in posterior temporal gyri of especially the right hemisphere (#4), as well as in bilateral inferior parietal lobules. Interactions of stimulus length and group were all lateralized to the left hemisphere. More specifically, in the middle occipital gyrus (#6) and in regions around the central sulcus (#5) controls tended to have stronger CVC than single letter signals, whereas dyslexics exhibited an opposite pattern. Of primary interest were effects involving the factor congruency. The main effect of congruency mode revealed stronger signals for incongruent stimuli in the left premotor cortex (#7) and middle temporal gyri. Stronger signals for congruent stimuli were observed in left posterior occipital and medial frontal gyri (#8), as well as in thalamic areas. Effects of congruency mode were modified by stimulus length in left cerebellar (#11), inferior temporal, and postcentral regions, as well as in the right postcentral gyrus (#12). The interaction of congruency mode and group mainly reflected increased signals to incongruent stimuli in controls in combination with an opposing pattern in dyslexics. Such interactions occurred in the left superior temporal (#9) and left fusiform gyri (#10), as well as the left calcarine sulcus and the right temporal pole. Of most interest were significant clusters of the three-way interaction (stimulus length by congruency mode by group). These were located in regions including the right STG / STS (#14) and left middle temporal gyrus (#13). ROI analyses in these regions revealed significant congruency mode by group interactions for CVC stimuli (right STG: $F(1,33) = 11.090$, $P < 0.01$; left MTG: $F(1,33) = 4.445$, $P < 0.05$) but not for single letters (right STG: $F(1,33) = 0.092$, n.s.; left MTG: $F(1,33) = 2.814$, n.s.). In both regions, there were significantly larger signals to incongruent than congruent CVCs in controls. Dyslexics showed a contrary pattern that was significant in the right STG cluster. The

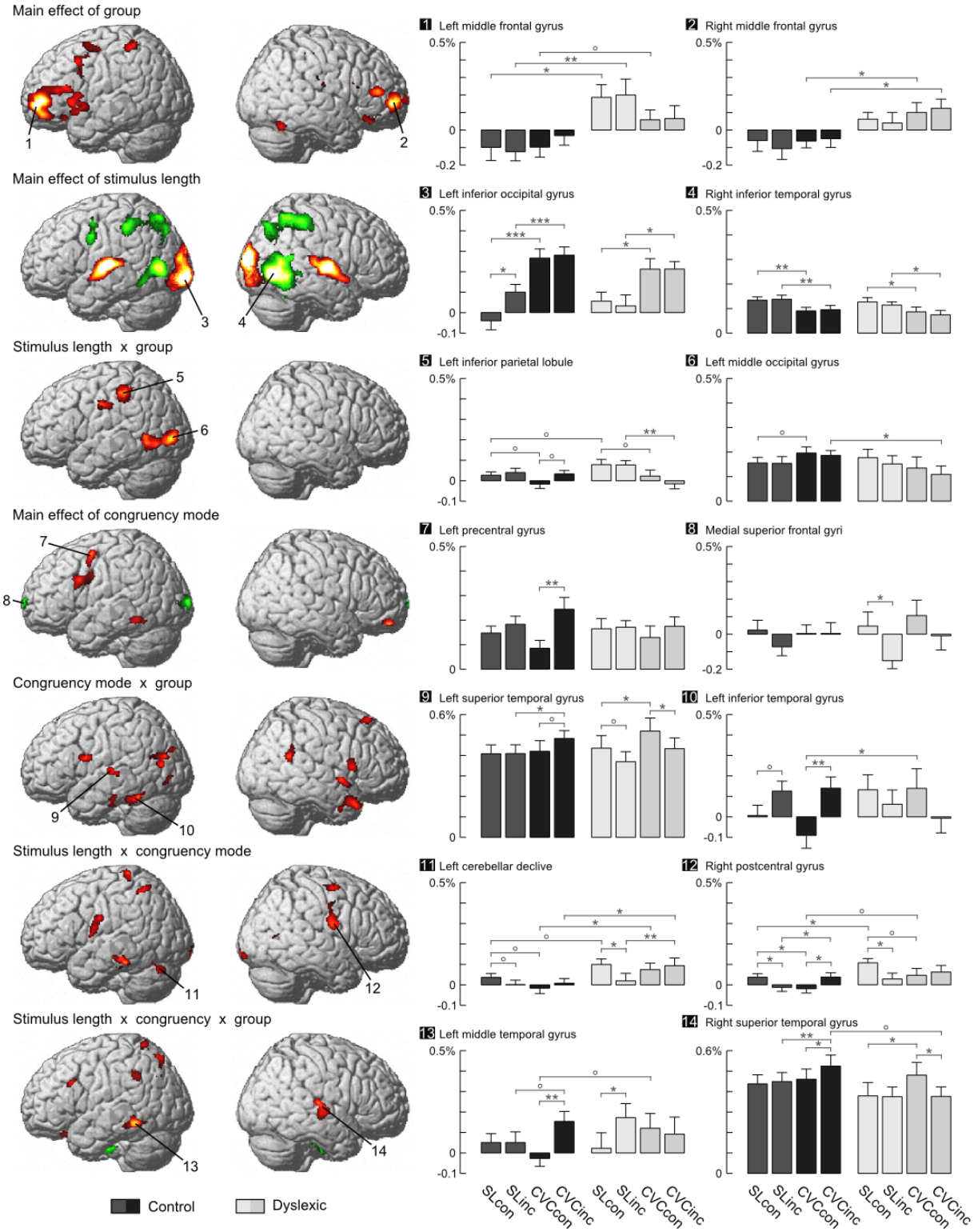


Figure 5.2 Brain renders of the three-way repeated measures ANOVA on the four bimodal AV stimulus conditions (cf. Table 5.2, p. 60). Positive and negative effects of the comparisons are colour-coded in red and green. Threshold at $P < 0.005$ voxelwise, cluster extent $k \geq 160$. To the right of the brain renders, mean percent signal change of spheres around peak voxels of selected significant clusters is depicted and post-hoc *t*-test are indicated. °$P < 0.1$, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, error bars represent 1 SEM. Corresponding MNI coordinates of significant clusters are listed in Table 5.3 (p. 69). Abbreviations: SLcon = congruent single letter stimuli, SLinc = incongruent single letter stimuli, CVCcon = congruent consonant-vowel-consonant stimuli, CVCinc = incongruent consonant-vowel-consonant stimuli.

Table 5.3 Peak points (MNI coordinates and corresponding brain regions) within significantly activated clusters of the stimulus length x congruency mode x group repeated measures ANOVA (cf. Table 5.2, p. 60) depicted in Figure 5.2 (P<0.005, k≥160).

			MNI (x y z)	*Z*-score	Volume (mm³)
Main effect of group					
Dyslexic > Control					
Frontal	L	Middle / Superior Frontal Gyrus	-37 56 -2	5.04	14516
	L	Middle Frontal Gyrus / Sub-Gyral	-43 14 45	3.12	3011
	L	Middle Frontal / Precentral Gyrus	-33 0 59	3.05	722
	R	Cingulate Gyrus	14 9 38	4.25	6669
	R	Middle Frontal Gyrus	35 54 2	3.76	4178
	R	Inferior Frontal Gyrus	48 42 12	3.59	1522
	R	Paracentral Lobule / Precentral / Postcentral Gyrus	17 -34 51	3.20	1873
	R	Inferior Frontal Gyrus / Sub-Gyral	36 2 21	3.13	786
	R	Inferior / Middle Frontal Gyrus	17 41 -18	3.06	1269
	R	Paracentral Lobule	5 -25 50	3.03	776
	R	Superior Frontal Gyrus	12 69 3	3.00	557
Parietal	L	Postcentral Gyrus / Superior Parietal Lobule	-31 -40 59	3.39	1607
	R	Inferior Parietal Lobule	41 -24 29	3.52	635
Temporal	R	Fusiform Gyrus	47 -60 -24	3.30	712
Cerebellum	R	Cerebellar Declive / Pyramis	17 -75 -29	3.17	678
Main effect of stimulus length					
CVC > SL					
Temporal	L	Superior Temporal Gyrus	-63 -16 8	5.63	12832
	R	Superior Temporal Gyrus	62 -10 3	4.90	13331
Occipital	L	Lingual / Inferior / Middle Occipital Gyrus	-15 -96 -9	6.21	17371
	R	Lingual / Middle Occipital Gyrus / Cuneus	21 -91 2	6.47	15265
SL > CVC					
Frontal	L	Inferior / Middle Frontal / Precentral Gyrus	-36 -1 36	4.17	3230
Temporal	L	Middle Temporal Gyrus / Inferior Parietal Lobule	-46 -67 6	4.07	22424
	R	Inferior / Middle Temporal Gyrus	42 -57 -6	4.91	36285
Stimulus length x group					
Control(CVC – SL) > Dyslexic(CVC – SL)					
Frontal	L	Precentral / Postcentral Gyrus	-43 -10 36	3.52	1775
Parietal	L	Inferior Parietal Lobule / Postcentral Gyrus	-39 -37 45	3.70	3335
Occipital	L	Middle Occipital Gyrus / Cuneus	-42 -55 0	4.01	8546
	L	Cuneus / Calcarine Sulcus	-1 -87 3	3.18	810
Sub-lobar	R	Calcarine Sulcus	27 -61 5	3.43	638
Main effect of congruency mode					
Incongruent > congruent					
Frontal	L	Middle Frontal / Precentral Gyrus	-43 0 56	3.25	1316
	L	Inferior / Middle Frontal / Precentral Gyrus	-49 14 30	3.10	2460
	R	Middle Frontal Gyrus (orbital part)	38 53 -17	4.08	749
Temporal	L	Middle Temporal Gyrus	-58 -46 -12	3.17	830
Congruent > incongruent					
Frontal	L	Superior Frontal Gyrus (medial part)	-4 68 8	3.92	1016
Occipital	L	Middle / Superior Occipital Gyrus / Cuneus	-18 -102 8	3.37	1353
Sub-lobar	L/R	Extra-Nuclear / Thalamus	-3 -30 14	3.72	3105
Congruency mode x group					
Control(incongruent – congruent) > Dyslexic(incongruent – congruent)					
Frontal	L	Inferior Frontal / Precentral Gyrus	-52 0 20	3.35	911
	R	Precentral Gyrus	59 14 9	3.48	807
	R	Superior Frontal Gyrus (medial part)	14 30 60	3.47	675
Temporal	L	Fusiform Gyrus / Inferior Temporal Gyrus	-52 -40 -26	3.70	1384
	L	Middle Temporal / Gyrus	-45 -73 12	3.62	2271
	L	Superior Temporal Gyrus	-67 -21 6	3.42	810

	L	Inferior Temporal / Fusiform Gyrus	-48 -22 -24	3.17	560
	R	Middle / Superior Temporal Gyrus	45 17 -29	3.67	1775
	R	Superior Temporal Gyrus	57 2 -5	3.51	932
	R	Superior Temporal Gyrus / Sub-Gyral	41 -48 21	3.31	1667
Occipital	L	Lingual / Inferior Occipital Gyrus / (Pre-)Cuneus	-19 -70 3	3.36	4077
	L	Lingual Gyrus	-6 -88 -6	3.06	638
Sub-lobar	R	Extra-Nuclear / Precuneus / Cingulate Gyrus	17 -45 5	3.28	1742
Stimulus length x congruency mode					
SL(congruent – incongruent) > CVC(congruent – incongruent)					
Frontal	L	Pre- / Postcentral	-63 -3 15	3.08	1384
	R	Middle Frontal / Precentral Gyrus	47 -4 60	3.67	776
	R	Pre- / Postcentral	63 -9 24	3.50	2072
Parietal	L	Paracentral Lobule / Postcentral Gyrus	-25 -37 75	3.23	874
	L	Inferior Parietal Lobule	-45 -57 59	3.08	901
Temporal	L	Inferior / Middle Temporal Gyrus	-69 -37 -20	3.26	1519
Occipital	L	Cuneus / Calcarine Sulcus	-3 -105 -14	3.46	557
	R	Inferior Occipital / Lingual Gyrus	27 -99 -12	3.33	540
Cerebellum	L	Cerebellar Declive	-34 -73 -27	3.30	1063
	L	Cerebellar Culmen	-6 -61 -8	3.14	935
Stimulus length x congruency mode x group					
Control(CVCinc – CVCcon) > Dyslexic(CVCinc – CVCcon); Dyslexic(SLinc – CVCinc) > Control(SLinc – CVCinc)					
Frontal	L	Rectal / Inferior / Middle Frontal Gyrus	-10 30 -23	3.24	601
	L	Inferior / Middle Frontal Gyrus / Sub-Gyral	-36 23 29	2.96	550
Parietal	L	Inferior Parietal Lobule	-64 -49 41	3.36	581
	L	Postcentral Gyrus / Precuneus	-15 -55 69	3.30	648
	L	Superior Parietal Lobule / Precuneus	-16 -69 59	3.01	1094
Temporal	L	Inferior / Middle Temporal Gyrus	-67 -48 -12	3.45	1833
	L	Superior Temporal Gyrus	-36 -40 9	3.10	655
	R	Superior Temporal Gyrus	69 -16 0	3.58	2045
Dyslexic(CVCinc – CVCcon) > Control(CVCinc – CVCcon); Control(SLinc – CVCinc) > Dyslexic(SLinc – CVCinc)					
Pons	L/R	Brainstem (Pons)	-6 -16 -41	3.76	1070

CVC = consonant-vowel-consonant stimuli, SL = single letter stimuli, SLcon = congruent single letter stimuli, SLinc = incongruent single letter stimuli, CVCcon = congruent consonant-vowel-consonant stimuli, CVCinc = incongruent consonant-vowel-consonant stimuli, L = left, R = right

pattern of significances in an additionally tested contralateral STG ROI (-69 -16 0) was identical to that of the right STG, but it did apparently not surpass the overall statistical threshold of the three-way ANOVA (compare #9 for a very similar ROI).

Similar ROI analyses were also conducted in regions that have previously been forwarded as AV or multisensory integration sites by studies that included congruent and incongruent AV conditions (Blau et al., 2010; Blau et al., 2009; Hocking & Price, 2008; Pekkola et al., 2006; van Atteveldt et al., 2004). Within the majority of these ROIs, there were effects for the CVC stimuli but not for single letter stimuli. More specifically, larger activation for incongruent than congruent CVCs was again obtained for controls but not dyslexics in bilateral middle (van Atteveldt et al., 2004), and posterior superior temporal sulci (Hocking & Price, 2008), as well as in right anterior STG (Blau et al., 2010). For a complete listing of these comparisons and the corresponding MNI coordinates see supplementary Table 5.7 (p. 97).

The most important finding within this section is a reversed effect in dyslexics compared to controls in bilateral STS / STG, regions that are associated with AV integration.

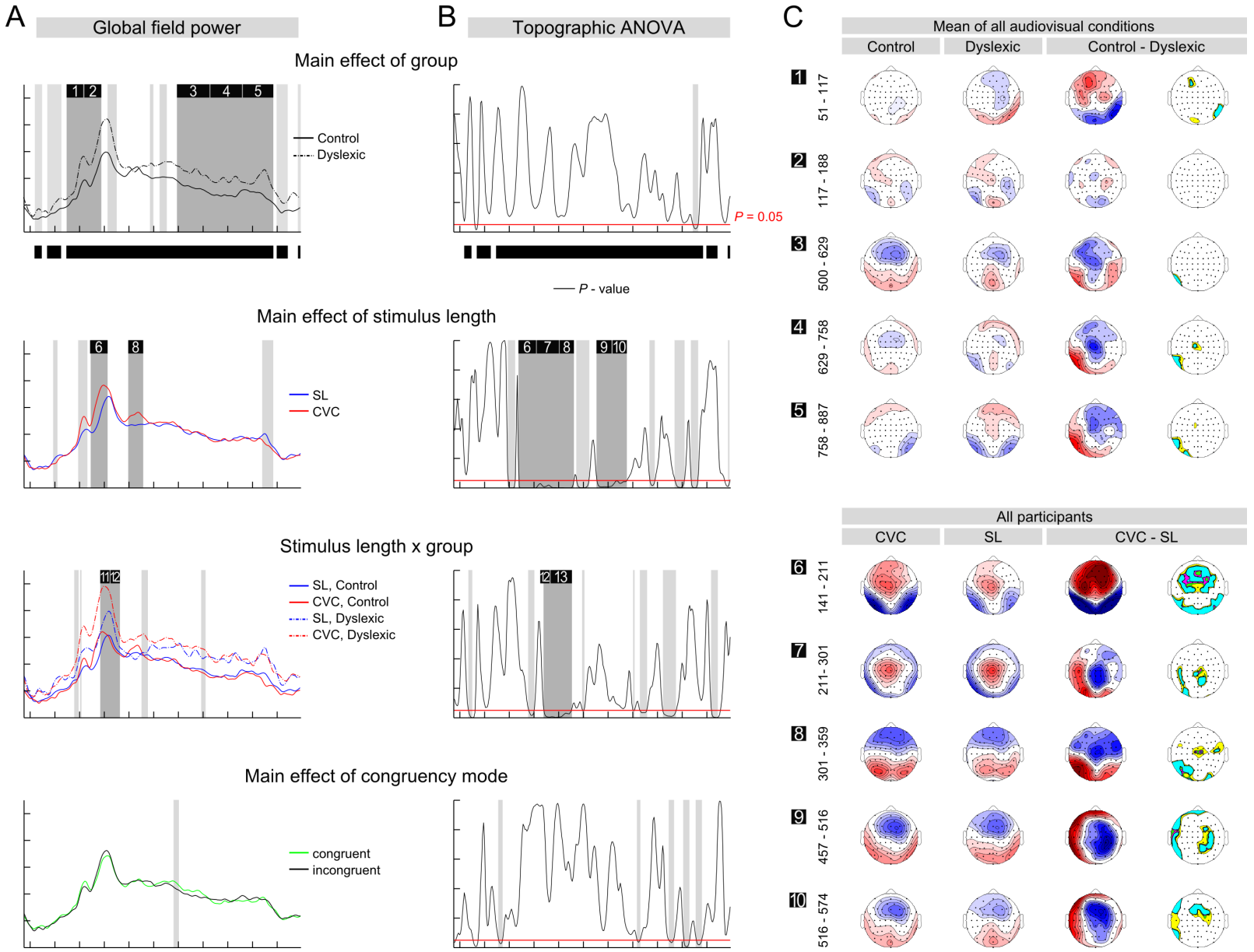
EEG

Across all participants, topographic consistency for the four bimodal AV conditions was given most of the time (see legend of Figure 5.3, p. 72), including an extensive post-stimulus period from 51 ms to 887 ms that encompasses all the results described subsequently. The analysis of global field power (Figure 5.3A) revealed main effects of group in the P1 time window (53 – 160 ms) and from 500 to 887 ms (late P2 phase and visual offset negativity). Within these segments dyslexics consistently showed a higher GFP than controls. Further inspection by means of topographic contrasts (Figure 5.3C, #1) showed frontal and occipital differences during the P1. During the transition from P1 to N1 (#2) no spatially confined group differences were found. Later segments (#3 – 5) showed left occipitotemporal differences, reflecting stronger activity for the late P2 in controls on the one hand, and an earlier and stronger emergence of the visual offset negativity in dyslexics on the other hand.

Next, significant main effects of stimulus length with higher field strength to CVCs were observed during N1 (148 – 211 ms, #6) and P2 phases (301 – 359 ms, #8). The TANOVA revealed topographic effects for the same latencies, but also for the interval in-between (211 – 301 ms, #7), as well as for later segments (457 – 516 ms, #9 – 10). During the P2, effects were observed especially over the left hemiscalp, including superior temporal sites. The later segments suggested the gradual propagation of the occipitotemporal P2 positivity to temporal and eventually frontal sources. This propagation to anterior sites was more pronounced in CVCs than single letters, especially over the left hemiscalp (#9 – 10).

Interactions of group and stimulus length emerged during the N1 in the GFP analysis and for the N1 – P2 transition for the TANOVA. This latter effect seemed driven by an earlier emergence of the P2 in dyslexics compared to controls in the case of CVC stimuli (#12), as well as a generally stronger difference between CVCs and single letters in dyslexics compared to controls (#12 – 13).

No effects involving the factors congruency mode and group passed the duration threshold. A more liberal analysis of this core interaction is depicted and described in the supplement (Figure 5.10, p. 93). Hence, despite some convergence between EEG and fMRI data (especially in main effects of stimulus type), none of the analyses of primary interest, i.e. analyses involving the factor congruency mode, revealed striking ERP results.


A
Global field power
B
Topographic ANOVA
C
Main effect of group
1 2
3 4 5
Control
Dyslexic
P = 0.05
P - value
Main effect of stimulus length
6
8
6 7 8
9 10
SL
CVC
Stimulus length x group
11 12
12 13
SL, Control
CVC, Control
SL, Dyslexic
CVC, Dyslexic
Main effect of congruency mode
congruent
incongruent
Mean of all audiovisual conditions
Control
Dyslexic
Control - Dyslexic
1 51 - 117
2 117 - 188
3 500 - 629
4 629 - 758
5 758 - 887
All participants
CVC
SL
CVC - SL
6 141 - 211
7 211- 301
8 301 - 359
9 457 - 516
10 516 - 574

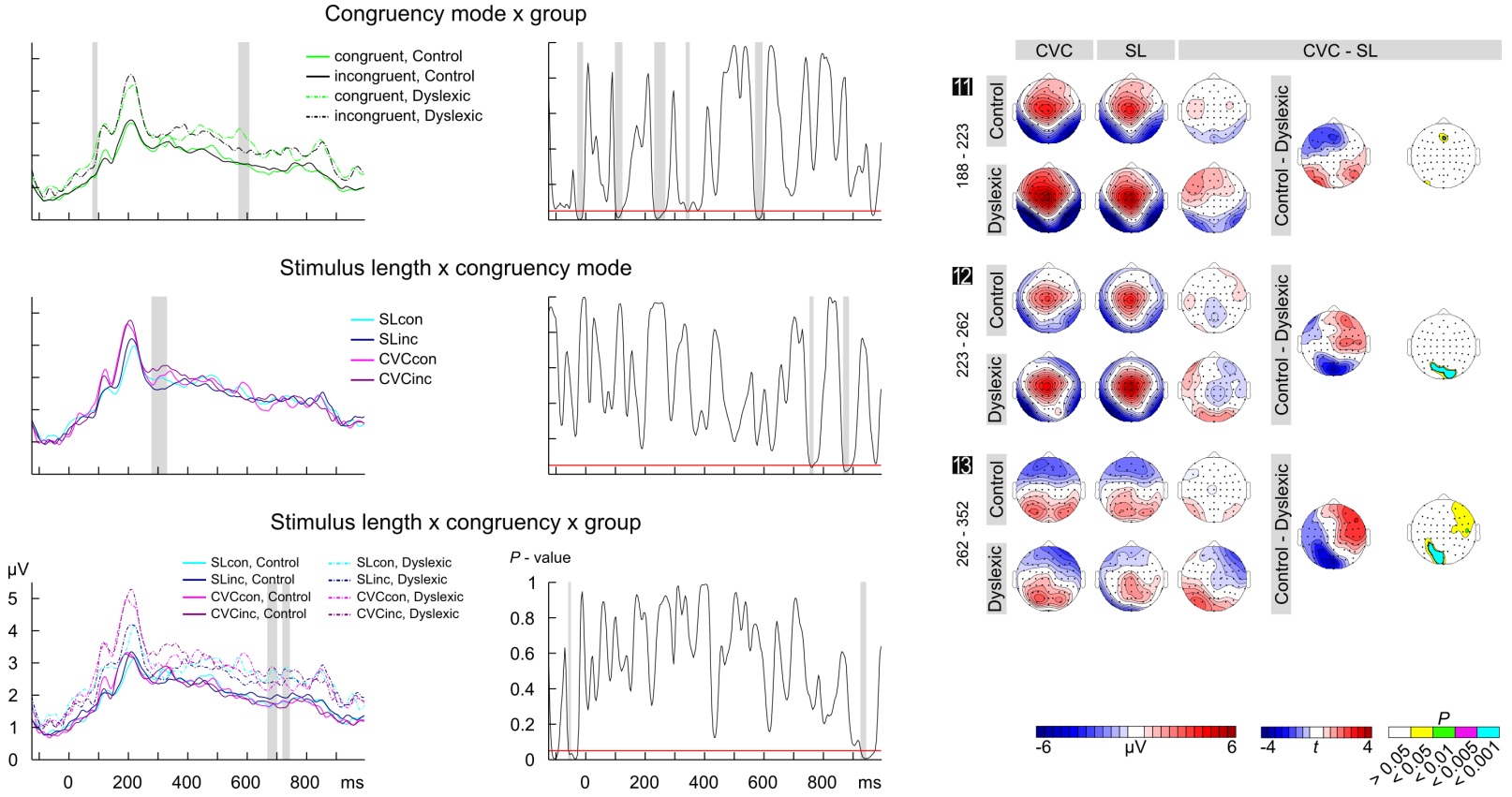


Figure 5.3 Results of global field power (A) and topographic ANOVA randomization statistics (B) of EEG data for the three-way repeated measures ANOVA on the four bimodal AV stimulus conditions. Grey shading indicates significant time points ($P < 0.05$), dark grey shading indicates significant periods that also surpass adjustment for multiple comparisons (see 5.3.5 EEG Acquisition and Analysis, p. 61). Black bars below the uppermost graphs indicate periods of significant topographic consistency across all 35 participants. Dark grey periods are illustrated by means of topography displays (C). In (C), the left half depicts voltage maps of the conditions that evoked significant ANOVA effects. The right half depicts statistical comparisons (*t*- and *P*-maps) of these voltage maps. Time windows of these maps in milliseconds are indicated vertically on the left. Abbreviations: CVC = consonant-vowel-consonant stimuli, SL = single letter stimuli, SLcon = congruent single letter stimuli, SLinc = incongruent single letter stimuli, CVCcon = congruent consonant-vowel-consonant stimuli, CVCinc = incongruent consonant-vowel-consonant stimuli.

5.5 *Discussion*

The present study investigated neural mechanisms of automatized AV integration in typical and impaired readers at the developmentally important stage of adolescence. Audiovisual integration was probed by, firstly, assessing whether AV congruent stimulation triggers stronger activation than the sum of visual and auditory stimulation in isolation (super-additivity), and secondly by comparing activation to congruent and incongruent stimulation. One important novelty was the employment of more naturalistic reading material than mere letters, namely CVC stimuli. EEG and fMRI data were collected simultaneously in order to analyse both spatial and temporal aspects of AV processing and of impairments in DD.

In brief, group comparisons of congruency mode effects suggested aberrant phonetic AV integration for dyslexics in regions involved in reading such as the STG, especially in the case of CVC stimuli. Super-additivity assessments did not reveal reliable group differences, suggesting intact basic mechanisms of AV integration in dyslexics, including integration at the sensory level.

5.5.1 Super-additivity Effects and Basic Audiovisual Interactions

Previous studies have advocated left and right STS and PT as sites of multisensory integration, based on stronger responses to bimodal AV stimulation compared to the summed unisensory responses (Calvert, et al., 2000; van Atteveldt, Formisano, Blomert, et al., 2007; van Atteveldt, et al., 2004). In the present study, the criterion of super-additivity [CVCcon > (CVCa + CVCv)] was never met in any group. In fact, there was a range of highly significant clusters for the inverse contrast (i.e. sub-additivity), including the left posterior STG (cf. T. M. Wright, et al., 2003, who have found partial STG sub-additiviy and partial super-additivity). The results are therefore inconclusive in delineating sites of multisensory integration and support the inconsistent picture of previous fMRI literature on super-additivity as summarized by Hocking and Price (2008). Importantly however, there were no significant group differences for any of these comparisons.

Interestingly, previous electrophysiological studies have consistently reported sub-additivity for AV congruent stimulation (Besle, et al., 2008; Besle, et al., 2004; Jost, Eberhard-Moscicka, Frisch, Dellwo, & Maurer, 2014; Klucharev, et al., 2003; Möttönen, Schürmann, & Sams, 2004; Raij, et al., 2000; van Wassenhove, Grant, & Poeppel, 2005). The present EEG data similarly showed sub-additive effects of GFP across both groups. Topographic maps further revealed sub-additive effects at left superior temporal electrodes across both groups

between 230 and 300 ms. Such effects might originate from neurons that are oriented perpendicular to the scalp surface and which have been localized to the STG (Scherg & von Cramon, 1985, 1986). Sub-additivity could be the result of efficient tuning to audiovisually matching input, where processing of redundant information is minimized by cross-modal inhibition mechanisms (Raij, et al., 2000; van Wassenhove, et al., 2005).

Previous studies using lip movements and speech sounds have observed effects around this latency in auditory cortices and STS (Klucharev, et al., 2003; Möttönen, et al., 2004; van Wassenhove, et al., 2005). Intracranial recordings in humans have also revealed sub-additivity, although at slightly earlier latencies (Besle, et al., 2008). In fact, latencies after around 200 ms are much more likely to be confounded in a qualitative fashion by non-sensory processes (e.g., Hillyard, et al., 1998), such as attentional or motor processes. Such confounds compromise a valid application of the super-additivity criterion. The observed topographic sub-additive effects after 230 ms therefore need to be treated with caution.

Earlier ERP effects that emerged during the P1 phase even showed some modulation by group. Besides the fact that none of these earlier effects passed the adjustment for multiple comparisons, this modulation was mainly driven by group differences already at the level of the unimodal conditions. This was also observed for later occipitotemporal group differences (Figure S5). Hence, robust group effects for the super-additivity criterion were absent also in EEG data. Group differences at the level of unimodal visual and auditory processes are in line with previous findings. Theories on visual deficits range from basal deficits in visual pathways (Demb, Boynton, & Heeger, 1998; Stein, 2001; Vidyasagar & Pammer, 2010) to impaired tuning to letters or print (Kronschnabel, et al., 2013; Maurer, et al., 2007; Maurer, et al., 2011). Theories in the auditory domain have suggested abnormal neural representations of brief and rapidly successive sensory inputs (Nagarajan, et al., 1999; Renvall & Hari, 2002; Tallal, 1980), in line with the observed group differences in auditory working memory (see Table 5.1, p. 57). The possibility that deficits in the unimodal domain are primary to the development of reading difficulties while phonological deficits either are a secondary or an independent cause is still an unresolved issue. Especially impairments in mechanisms of visuospatial attention have repeatedly been confirmed (Bosse, Tainturier, & Valdois, 2007; Buchholz & Aimola Davies, 2007; Facoetti, Ruffino, Peru, Paganoni, & Chelazzi, 2008; Valdois, Bosse, & Tainturier, 2004; Vidyasagar, 2013; but see also Skottun & Skoyles, 2006). In this context, a multiple deficit perspective and the acknowledgement of various subtypes of DD have been suggested (for a recent review, see Peterson & Pennington, 2012).

Taken together, the present data do not provide convincing evidence for general deficits in

AV integration in dyslexia. At first sight this seems in contrast to what has recently been suggested by Widmann et al. (2012; see 5.2 Introduction, p. 53). Yet, although these authors used nonverbal stimulus material, their findings are, as they mention themselves, compatible with a deficit in the dynamic construction of symbol–sound correspondences. Super-additivity, however, does not test such “grapho-phonological” mechanisms in first place but rather general and more basic aspects of AV integration. Further evidence for intact basic AV integration in dyslexics comes from the present target detection task. Behavioural data revealed faster reaction times for AV targets compared to unimodal targets in both groups. This AV facilitation has been found to reflect combined processing of the auditory and visual input (“coactivation model”; Miller, 1986; also see Besle, et al., 2004; Raij, et al., 2000; Schröger & Widmann, 1998) rather than separate processing with the quicker of the two inputs initiating a motor response ("race model"; Raab, 1962). The absence of group differences in this detection task indicates that overt indicators of basic AV integration are intact in our dyslexic sample. Accordingly, we believe that a deficit in general crossmodal processing abilities should cause more severe behavioural disruptions than impaired reading. Yet, further investigations are certainly needed to consolidate this claim.

5.5.2 Congruency Effects and Phonetic Audiovisual Interactions

Differences in brain responses to congruent AV grapheme–phoneme stimulation and audiovisually incongruent stimulation indicate interactions at the phonetic level (Hocking & Price, 2008; Klucharev, et al., 2003; Ojanen, et al., 2005). Such interactions have been interpreted in terms of AV integration (Blomert, 2011; van Atteveldt, et al., 2004; van Atteveldt, Formisano, Goebel, et al., 2007). They cannot be explained by different processing of the individual unimodal conditions because these are the same across congruent and incongruent conditions. The most prominent main effects of congruency mode in our fMRI data emerged in left premotor areas and left dorsal opercular parts. Across all subjects there were stronger responses for incongruent than congruent stimuli (subsequently referred to as incongruency effect). Incongruency effects have previously been reported for these regions in multisensory studies (Pekkola, et al., 2006; van Atteveldt, Formisano, Blomert, et al., 2007). The dorsal opercular part shows mirror neuron properties (Molnar-Szakacs, Iacoboni, Koski, & Mazziotta, 2005) and is significantly active during speech observation, listening, and imitation (D. E. Callan, Callan, Gamez, Sato, & Kawato, 2010; Iacoboni, 2008; Osnes, Hugdahl, & Specht, 2011; Wilson, Saygin, Sereno, & Iacoboni, 2004), but also during reading (Hagoort, et al., 1999; Price, et al., 2006). It has been associated with processing prior to articulatory recoding

(Papoutsi, et al., 2009; Price, 2012). Higher activation for incongruent stimulation might be the result of increased overall input due to twice the phonetic information as compared to congruent pairings. Note that the observed premotor effects do not reach into the medially located anterior cingulate cortex, an area associated with conflict processing (e.g., Botvinick, Cohen, & Carter, 2004).

Modulations by group

A smaller patch in ventral opercular parts (part of Broca's area) showed group-specific congruency mode effects with stronger responses to incongruent than congruent stimuli in controls, whereas dyslexics exhibited the reversed pattern (i.e. congruency effects). Ventral parts of the inferior frontal gyrus have been associated with the mapping of heard or read speech to articulation (Chang, Kenney, Loucks, Poletto, & Ludlow, 2009; Papoutsi, et al., 2009). The same pattern of group differences was also observed in the left inferotemporal cortex which also has been associated with grapho-phonological processing (Cai, Paulignan, Brysbaert, Ibarrola, & Nazir, 2010; Price & Devlin, 2011). Both functional and structural disruptions in inferotemporal regions and the fusiform gyrus are well-documented for dyslexia (Linkersdörfer, Lonnemann, Lindberg, Hasselhorn, & Fiebach, 2012; Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008; Richlan, et al., 2011). Another cluster was located around the parieto-temporal-occipital junction (Brodmann area 39) where integration of multimodal input is thought to take place (Beauchamp et al., 2004; Booth, et al., 2002; A. M. Callan, Callan, & Masaki, 2005) and which has early been considered disrupted in dyslexia (Shaywitz, et al., 1998). The interaction cluster in the right temporal pole was rather unexpected. However, this region is part of the early auditory processing streams (Galaburda & Sanides, 1980) and a number of studies have shown its involvement in AV integration (Kreifelts, Ethofer, Grodd, Erb, & Wildgruber, 2007; Olson, Gatenby, & Gore, 2002; Robins, Hunyadi, & Schultz, 2009). Importantly, the left PT (Figure 2, bar chart #9) also exhibited incongruency effects in controls but congruency effects in dyslexics. The ROI in the contralateral STG / STS (Figure 2, #14) showed further modulations by stimulus length: group-specific effects of congruency mode were only apparent for CVC but not single letter stimuli. Hence, in sites that have frequently been associated with grapho-phonological conversion and multisensory integration (Jobard, Crivello, & Tzourio-Mazoyer, 2003; Simos, et al., 2000; van Atteveldt, et al., 2004; Wise, et al., 2001) impaired readers exhibited aberrant AV processing at the phonetic level. This group difference was more significant for the CVC stimuli than single letters, indicating that more naturalistic speech stimuli probe dyslexic aberrances with higher sensitivity. The

left STG cluster was in close proximity to circuits shown to be disrupted in dyslexia by a recent meta-analysis (Richlan, et al., 2011). An analoguous right hemisphere cluster was not observed in this meta-analysis. Bilateral STG / STS effects seem to be rather typical for AV studies (Blau, et al., 2010; Blau, et al., 2009; Hocking & Price, 2008; Olson, et al., 2002; Robins, et al., 2009; van Atteveldt, et al., 2004), which are relatively new in dyslexia research and which were therefore underrepresented in the meta-analysis by Richlan et al. (2011). With respect to AV studies, the observed superior temporal ROIs of both hemispheres were located very closely to the peaking voxels of incongruency effects in typical readers as reported by Hocking and Price (2008) and in good proximity to the average coordinates of congruency effects across typical readers reported by van Atteveldt et al. (2004). At slightly more posterior and medial parts of the PT, Blau et al. (2009, 2010) reported a lack of congruency mode effects for both dyslexic children and adults. However, typical readers in these studies did not exhibit stronger responses to incongruent but rather to congruent stimuli (single letters and phonemes). In other words, typical readers in Blau et al. (2009, 2010) exhibited congruency effects that were similar to the CVC processing of dyslexic readers of the present sample.

One factor known to affect the engagement of superior temporal sites of multisensory integration is active versus passive stimulus exposure. During explicit matching, bilateral STG responses to incongruent stimuli were found to exceed those to congruent stimuli (van Atteveldt, Formisano, Goebel, et al., 2007). Participants in Hocking and Price (2008) as well as Pekkola et al. (2006) had to actively monitor stimuli and also showed incongruency rather than congruency effects in STG regions. However, our task aimed at passive stimulus exposure according to previous designs (Blau, et al., 2010; Blau, et al., 2009; van Atteveldt, Formisano, Blomert, et al., 2007; van Atteveldt, et al., 2004; van Atteveldt, Formisano, Goebel, et al., 2007). Our fMRI results, however, point to active processing of congruency mode in typical adolescent readers, if the observed incongruency effects in speech related brain regions are taken as an indicator. Notably, this pattern of active processing was mainly observed for the CVC strings rather than for single letter stimuli used in previous studies. This may explain some apparent discrepancies, and suggests that CVCs are qualitatively different from single letters as to the stimulation of reading processes. Specifically, CVCs are readable entities and might inevitably trigger reading and grapho-phonological processes in fluent readers whereas single letters might not. Smaller responses to congruent CVCs in controls could, as suggested above, reflect efficient tuning to converging AV information where redundancies are downscaled. Moreover, the emergence of grapho-phonological processes for CVCs might have had spill-over effects on the single letter conditions and eliminated the congruency ef-

fects observed in previous contexts of more passive processing.

Dyslexics, on the other hand, showed congruency effects for CVCs in bilateral STG and a similar trend for single letters in the left STG. The reversal of effects between controls and dyslexics indicates aberrant processing of grapho-phonological input in dyslexics. This may suggest that CVC stimuli trigger reading and grapho-phonological processes (with potential spill-over effects on single letters) only in typical readers. In dyslexic readers, the CVC stimuli may instead foster processes related to integrating single letters and sounds without engaging grapho-phonological processes involving multiple entities.

Recent theories on learning to read have advanced the idea of an inverted-U shape of activation levels across three stages of learning. Specifically, the activation level is thought to be lowest prior to learning, highest during early learning phases, and then reduces with expertise. Although this theory has its origins in observations of the left vOT cortex (Brem, et al., 2010; Maurer, et al., 2006; Maurer, et al., 2011; Price & Devlin, 2011), it is not necessarily restricted to this area (Price, 2013). Dyslexic adolescents might therefore be in a phase where brain regions involved in reading and grapho-phonological conversion are sensitized but where an efficient tuning has failed. This premature sensitivity might especially be observed in a naturalistic context of congruent CVC stimuli due to the increased salience of grapho-phonological processing compared to single letters. Previous studies on DD have used single letters only and found equally large responses to congruent versus incongruent letters (Blau, et al., 2010; Blau, et al., 2009). Single letters therefore might fail to trigger reading related processes in dyslexics. This inefficiency interpretation, however, is highly speculative and further evidence for AV integration deficits for word-like stimulus material is certainly needed.

The three-way interaction in a left inferior to middle temporal region could relate to robust activation of this region in semantic processing (Price, 2012), but the anterior and posterior poles of it have also been associated with phonological processing in a meta-analysis by Vigneau et al. (2006). The present results support a role of this region in (grapho-) phonological processing. Note that this region is next to a cluster in the inferotemporal cortex with congruency mode by group effects and an anterior congruency mode by stimulus length interaction cluster. Hence, the anterior parts of inferior to superior posterior temporal gyri seem to constitute key regions for grapho-phonological processes.

EEG data did not reveal robust interactions of congruency mode and group in GFP and TANOVA analyses. However, the supplementary Figure 5.10 (p. 93) indicated such interactions at latencies including the late N1 phase. It is possible that these are a reflection of the

superior temporal effects observed in fMRI. However, these interpretations remain speculative, given that results are not adjusted for multiple comparisons and rather exploratory in nature (see supplementary chapter 5.8.3 Discussion of Congruency by Group Interactions Shown in Figure 5.10 on page 85 for a more detailed discussion).

Taken together, the group effects in bilateral STG / PT support deficits in grapho-phonological conversion and AV integration in DD. At least for fMRI, the more speech-like CVC stimuli proved more sensitive in yielding group differences.

5.5.3 Other Group Effects

Main effect of group

Most prominent main effects of group were observed in the frontopolar prefrontal cortex, reaching into inferior frontal regions in the left hemisphere. Whereas inferior frontal overactivation in dyslexics probably indicates greater use of motor-articulatory strategies during phonological encoding (Pekkola, et al., 2006), frontopolar differences are less clear. This latter region is involved in higher-order cognitive processes (Badre, 2008; Burgess, Gilbert, & Dumontheil, 2007) and has been associated with semantic processing in language studies (Price, 2012). However, it is probably still "one of the least well understood regions of the human brain" (Ramnani & Owen, 2004, p. 184) and shows activation "during the performance of just about any kind of task" (Burgess, et al., 2007, p. 888). Burgess et al. (2007) argue that one commonality of all these tasks might be the encouragement to mind-wandering, for example, by being easy and repetitive. Importantly, significant frontopolar activation was only observed in dyslexics, whereas controls tended to exhibit deactivation. This could again suggest that dyslexic adolescents were less focused, whereas controls engaged in more active stimulus monitoring. Although highly speculative due to the uncertainties regarding this region, this would fit with impaired grapho-phonological conversion mechanisms in dyslexics that prevent them from continuous monitoring of congruency mode. An alternative interpretation of increased attempts of semantic access in dyslexia is in our view unlikely, considering that the task was explained beforehand and that it was clear that no meaningful stimuli are involved.

ERP data also revealed main effects of group with constantly higher GFP in dyslexics. In line with fMRI data, also frontal differences between groups were observed at P1 latency. Later group differences (500 – 887 ms) complete the picture of a range of nonspecific (sensu across all bimodal conditions and without regional peaks) group effects. The observed earlier emergence of the visual offset negativity or, stated differently, a shorter P2 in dyslexics could

be the scope of future investigations. It might indicate decreased attempts to match the current visual stimulus with a stored representation (cf. Appelbaum, Liotti, Perez, Fox, & Woldorff, 2009). Considering the AV context, differences in auditory processing (Hari & Renvall, 2001; Renvall & Hari, 2002; Tallal, 1980) might also account for a shortened late occipitotemporal positivity in dyslexics (compare unimodal auditory processing in Figure 5.8, p. 90).

Interaction of group and stimulus length

Very robust effects were obtained for effects of stimulus length in both fMRI and EEG data. Indeed, these effects showed the clearest convergence across both neuroimaging techniques.

CVC stimuli elicited stronger activation in posterior occipital and lingual regions, regions that are robustly activated in early word and letter string processing (Jobard, et al., 2003; Wandell, 2011). This was observed in both fMRI and EEG data. The examination of regions with stronger responses to single letters revealed a right middle occipital to posterior inferior temporal cluster. This area has been associated with false font string (Kronschnabel, et al., 2013; Tagamets, et al., 2000), face (e.g., Allison, et al., 1999; Sergent, Ohta, & MacDonald, 1992), and object processing (e.g., Szwed, et al., 2011). Interestingly, contralateral left-hemisphere regions that are in proximity to regions associated with visual print processing (Jobard, et al., 2003) exhibited stronger activation to CVCs in controls but not dyslexics.

Late topographic differences of EEG data (around 400 – 600 ms) indicated that the processing of CVCs is characterized by stronger anteriorly-directed signal propagation than single letter processing, especially in the left hemisphere. Frontal and temporal brain regions have been found active during word processing at such latencies (Simos, et al., 2009). Hence, activation patterns for CVCs are reminiscent of word or letter string processing that also proceeds from left occipital to temporal and frontal brain regions (Bentin, et al., 1999; Jobard, et al., 2003; Simos, et al., 2002; Simos, et al., 2009).

Both the right-lateralization of single letters and the anteriorly directed left-hemispheric processing of CVCs once more suggests qualitative differences between the two stimulus types and indicates that CVCs might be more valid stimuli than single letters to probe realistic reading.

EEG data showed group-specific effects of stimulus length for N1 and P2 latencies. Dyslexic readers exhibited a significantly stronger and nonsignificantly shorter N1 especially in the CVC condition. Stronger N1 responses in dyslexia are unprecedented, but may actually be explained by the aforementioned inverted-U shape of activation levels across learning stages with highest activation for early stages of reading due to effortful processing. Visual

inspection also suggests that a shorter N1 may have previously been observed in dyslexia (Brandeis, et al., 1994) as well as in the processing of unfamiliar symbol strings compared to words in typical readers (Maurer, et al., 2007). Taken together, this is suggestive of less efficient occipitotemporal tuning to letter strings in dyslexia, as has repeatedly been suggested (for meta-analyses, see Richlan, et al., 2009, 2011; for grey matter abnormalities, see Kronbichler, et al., 2008).

5.5.4 Limitations and Outlook

The results in superior temporal gyri are in line with a monitoring deficit of congruency mode in dyslexic adolescents, but generally more passive stimulus processing accounts cannot be excluded. In other words, attentional factors with respect to congruency mode monitoring were not controlled in the present study (nor in previous ones, e.g. Blau, et al., 2010; Blau, et al., 2009). We believe, however, that a more passive task accomplishment would rather be the result of altered superior temporal responses than its cause. That is, impaired AV or grapho-phonological tuning in dyslexic participants prevents automatized active congruency mode monitoring. The reversed interpretation would make less sense because it implies general attentional deficits including group differences in the target detection task, which was not the case. Moreover, other aspects of stimulus processing that are primarily associated with subvocal articulatory processes were engaged to a similar or even higher degree in dyslexics, indicating that the stimuli were not entirely ignored. In conclusion, the pattern of results in our view implies a specific impairment in grapho-phonological conversion, especially at a word-like level. Future studies should nevertheless take greater care to control for attentional factors, e.g. by demanding explicit monitoring of congruency mode or maybe using priming paradigms that probe subconscious processing. A task relating to AV processing while directly reflecting deficits in DD might also be informative.

The fact that we did not find strong convergence between the EEG and BOLD results may partly be due to focusing on relatively early ERPs. Better convergence may well be obtained for later ERP components or for EEG oscillations in certain frequency bands. Still, the ERPs analysed here have proven sensitive to multisensory integration and congruency.

The present results provide the first evidence that basic and sensory mechanisms of AV integration are intact in dyslexia. However, such absence of evidence is not evidence of absence, and further studies on basic mechanisms of AV integration in dyslexia are definitely needed. A next step could be to test the super-additivity criterion in combination with a purely non-

linguistic task that uses, for example, environmental sounds or musical instruments to test AV integration.

5.6 Conclusion

Although the phonological deficit hypothesis is the most commonly accepted account on dyslexia (see 5.2. Introduction, p. 53), the exact nature of this deficit and its exact contribution to reading difficulties are still unresolved. More than 30 years ago, it had already been suggested that specifically impairments in grapheme-phoneme conversion hamper efficient reading (Snowling, 1980). It is surprising that only recently the importance of grapho-phonological or AV conversion for dyslexia has been emphasized by a number of studies that demonstrated aberrant neural responses of AV integration in dyslexia (Blau, et al., 2010; Blau, et al., 2009; Froyen, et al., 2011; Mittag, et al., 2012; Widmann, et al., 2012). The present findings support these previous studies and report neural substrates of impaired grapho-phonological conversion in adolescent dyslexics. Importantly, aberrances were observed in bilateral superior temporal gyri and sulci, regions whose involvement in AV integration is well-documented (e.g., van Atteveldt, et al., 2004). Group differences were more pronounced for CVC stimuli than for single letters. The present study provides the first direct comparison of CVC and single letter stimuli in an AV context. Hence, dyslexia is characterized by AV deficits especially in a context of naturalistic speech- and word-like stimulation. These results were interpreted to reflect efficient tuning to congruent AV speech-like input in controls but dysfunctional or effortful processing in dyslexics. They are therefore in agreement with theories on learning to read that postulate an inverted-U shape of activation levels across proficiency levels (Price & Devlin, 2011). They are also in line with augmenting evidence for impairments in the access to phonological representations rather than their storage (Boets, et al., 2013; Ramus, 2014).

The present findings also indicate that dyslexic adolescents do not significantly differ from typical readers in general measures of AV integration, i.e. in super-additivity measures. This is in line with the specific deficits of this group, considering that general and more basic deficits in multisensory integration would probably result in more severe disruptions.

To summarize, the present study provides critical evidence that phonological deficits in dyslexia might be related to impaired AV mechanisms of grapho-phonological conversion, especially at the speech- and word-like level. Moreover, demonstrations of AV deficits in an adolescent sample are unprecedented.

5.7 Acknowledgements

This research was supported by the Swiss National Science Foundation [grant number 32_125407]. We are grateful to our participants and their families. We also would like to thank the physics and radiology teams of Children's Hospital Zurich for their kind assistance, as well as Raffaella Schmid, Lea Meier, Martina Liechti, and Katharina Schorscher for assistance with stimulus construction, data recordings and data preprocessing.

5.8 Supplementary Material

5.8.1 Details on Stimulus Material

There were 15 different letters (a, e, i, o, u, ü, d, g, k, l, n, p, r, s, t) and 18 CVCs (dal, düp, ged, gok, kal, kut, lar, lut, nüp, nug, ped, pok, rin, rün, sis, sor, teg, tis). In the bimodal incongruent conditions mismatching acoustic and visual stimuli were randomly assigned. It was ensured that in incongruent CVCs at least the beginning letter and phoneme of each sequence mismatched.

Durations of the sounds ranged between 140 ms and 530 ms (mean phonemes ≈ 260 ± 80 ms, mean CVCs ≈ 430 ± 80 ms). Loudness (intensity) was at a comfortable level and was held constant across acoustic stimuli according to the "BS. 1770-1" recommendation of the International Telecommunication Union (ITU-R, 2007).

CVCs extended over an average horizontal visual angle of 2.2 degrees.

5.8.2 Details on Electrode Positions and Impedances

Electrode positions were according to the international 10-20 system with additional electrodes at AF1/2, AFz, C1/2/5/6, CP1/2/3/4/5/6, CPz, F5/6, FC1/2/3/4/5/6, FCz, FPz, FT7/8/9/10, Iz, Oz, P5/6, PO1/2/7/8/9/10, POz, TP7/8/9/10). O1/2 and FP1/2 were placed 2 cm laterally of the standard positions for more even coverage. Electrooculogram (EOG) was recorded by two electrodes placed below the outer canthus of each eye. Electrocardiogram (ECG) was derived by attaching further electrodes to the right of the sternum and on the left chest underneath the heart. Safety resistors of 5 kΩ or 15 kΩ are applied on scalp or EOG / ECG electrodes, respectively. Total electrode impedances were kept below 25 kΩ or 35 kΩ, respectively. Total impedances of reference and ground electrodes were kept below 10 kΩ.

5.8.3 Discussion of Congruency by Group Interactions Shown in Figure 5.10

Figure 5.10 (p. 93) revealed effects of congruency mode in controls but not dyslexics at P1 latencies for left occipitotemporal electrodes. Phonological processing has been shown to emerge as early as 80 ms post stimulus (Ashby, Sanders, & Kingston, 2009). Still, it seems unlikely that such processes feed back to occipital P1 generators as soon as around 100 ms. Alternatively, differences in spatial attention are known to affect P1 amplitude (Luck, Woodman, & Vogel, 2000). Hence, controls but not dyslexics might have been more focused

in the context of congruent stimulation. As indicated above, dyslexics might have been in a generally more passive state.

There also were group by congruency interactions in the late N1 phase that are more likely to reflect differences in grapho-phonological conversion. The N1 to print stimuli is generated in occipitotemporal cortices (Allison, Puce, Spencer, & McCarthy, 1999; Maurer, Brandeis, & McCandliss, 2005; Maurer, Brem, Bucher, & Brandeis, 2005; Nobre, Allison, & McCarthy, 1994; Tarkiainen, Helenius, Hansen, Cornelissen, & Salmelin, 1999) and activity in such regions has been suggested to interact with regions associated with phonological processing (Price & Devlin, 2011; Richardson, Seghier, Leff, Thomas, & Price, 2011; Twomey, Kawabata Duncan, Price, & Devlin, 2011). It is also possible that the superior temporal effects observed in fMRI contribute to these group differences (in line with most extended N1 group differences at electrode TP9). Nevertheless, these interpretations remain speculative, given that results are not adjusted for multiple comparisons and rather exploratory in nature.

5.8.4 Supplementary Figures

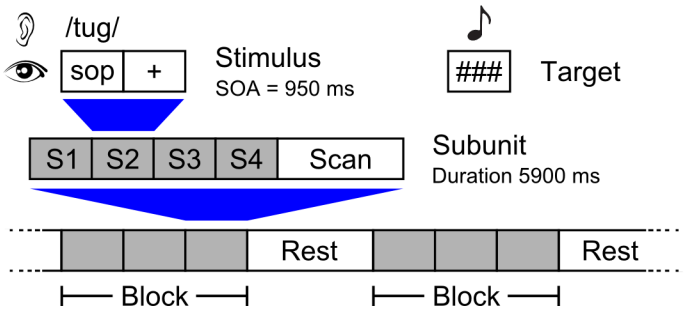


Figure 5.4 Illustration of the experimental paradigm. Subunits consisted of four stimuli (example: audiovisual incongruent CVCs) and three subunits formed a block. Targets were interspersed at any position within a subunit. Whole-brain fMRI scans were acquired at the end of each subunit and every 5900 ms, also during resting periods. Abbreviations: SOA = stimulus onset asynchrony.

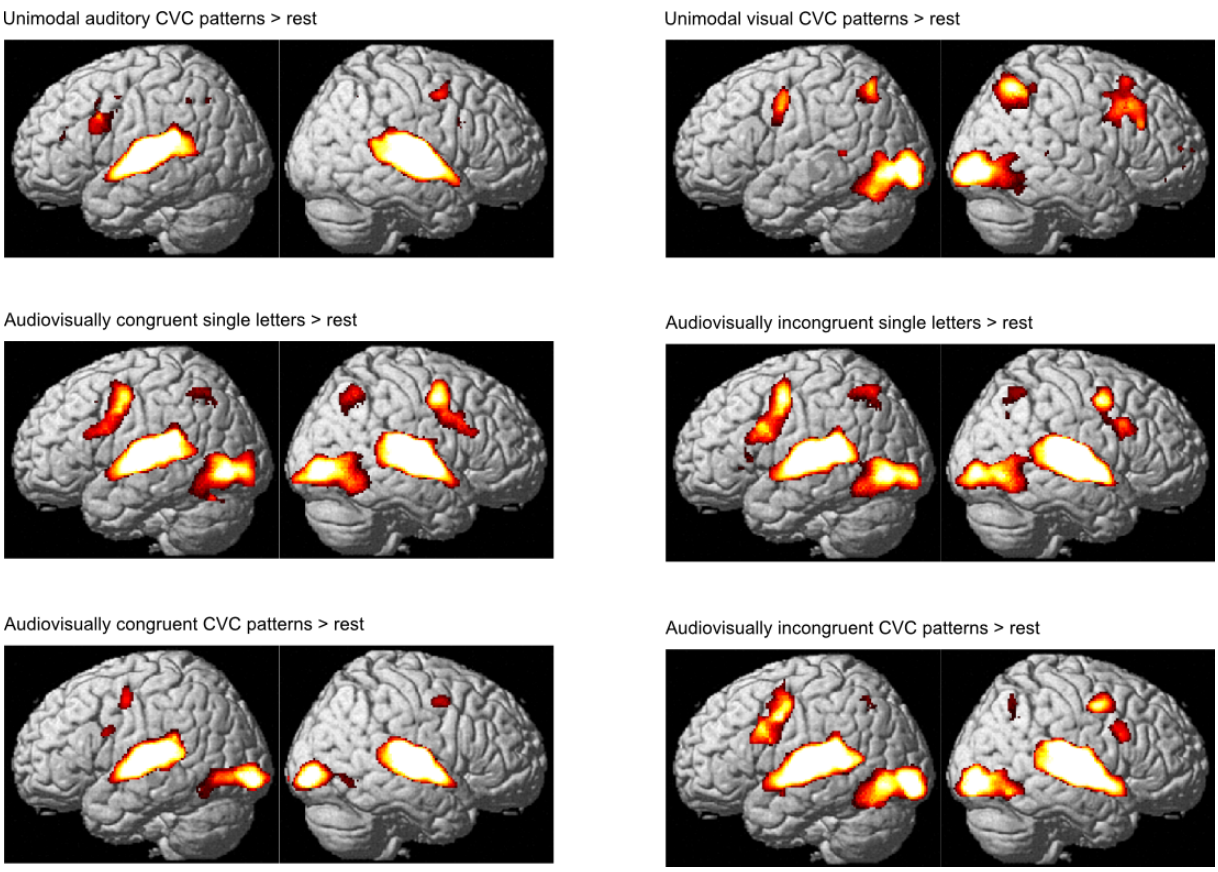


Figure 5.5 Brain renders of fMRI activation of all experimental conditions against rest across all 35 participants (control and dyslexic). Threshold at $P < 0.05$, FWE corrected. Abbreviations: CVC = consonant-vowel-consonant stimuli.

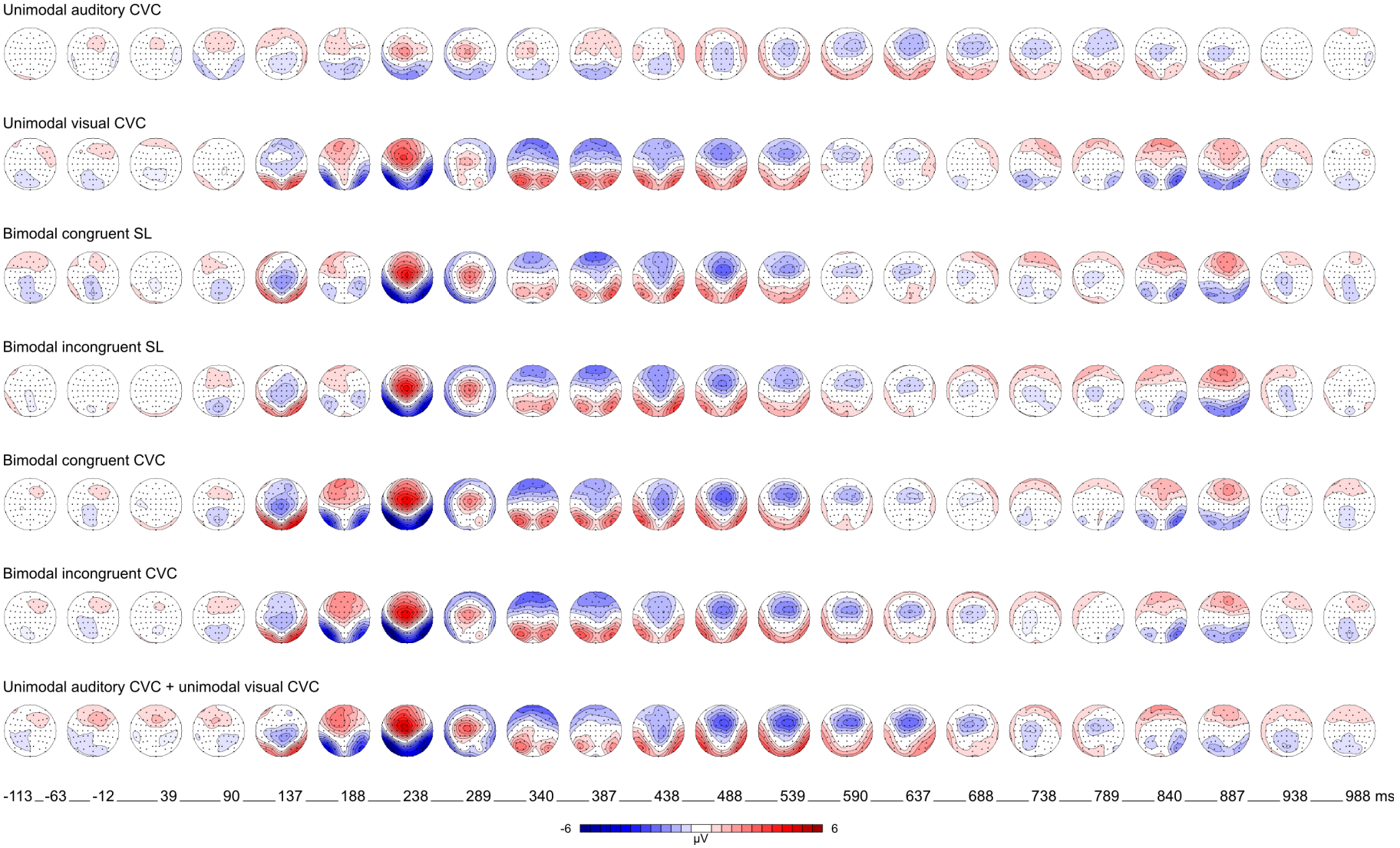


Figure 5.6 Basic EEG activation patterns. Mean voltage map series across all 35 participants (control and dyslexic) for all experimental conditions. Time line at the bottom indicates the time windows that have been averaged. The components P1 (ca. 80 – 150 ms), N1 (150 – 270 ms), and P2 (ca. 270 – 550 ms) are evident in all conditions involving visual stimulation. Abbreviations: CVC = consonant-vowel-consonant stimuli, SL = single letter stimuli.

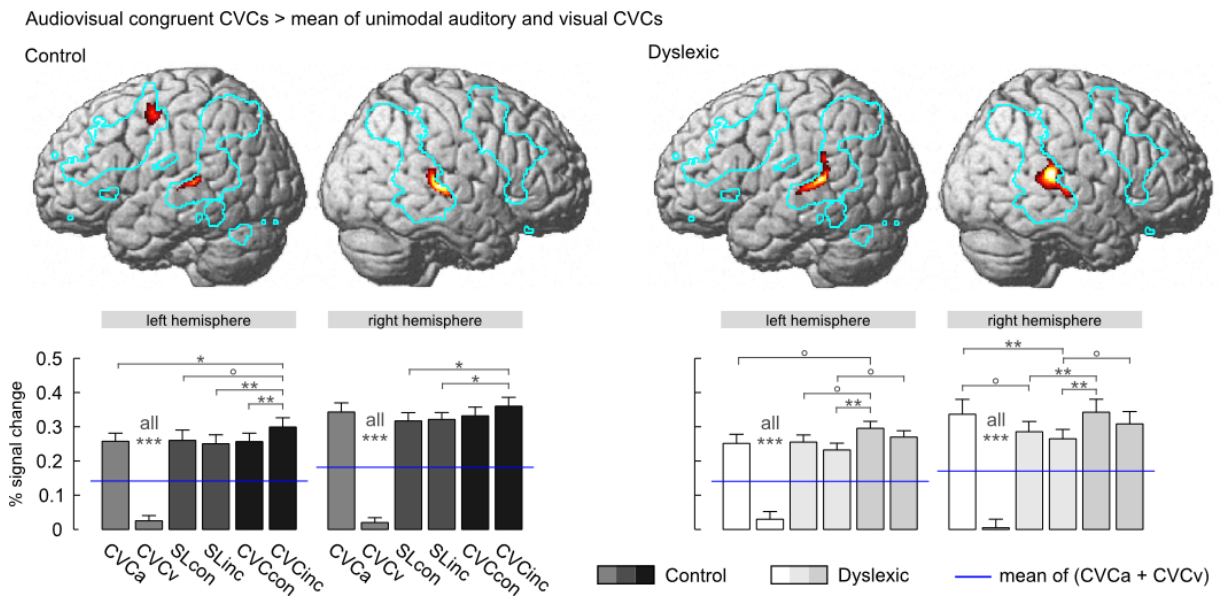
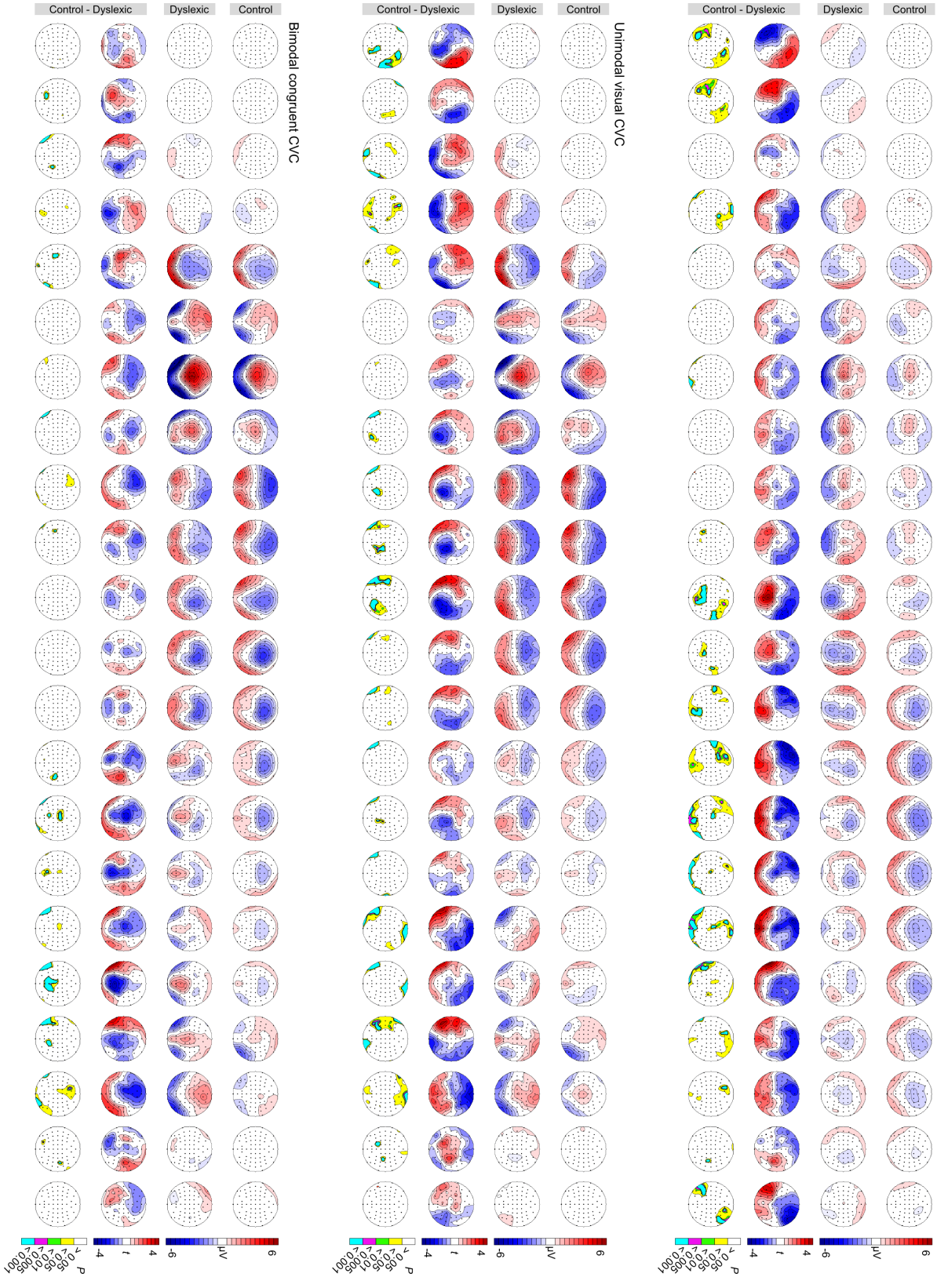


Figure 5.7 Brain renders of the relaxed super-additivity criterion for control (left panel) and dyslexic participants (right panel): congruent CVC stimuli contrasted against the mean of unimodal auditory CVCs and unimodal visual CVCs. Threshold at $P < 0.005$ voxelwise, cluster extent $k \geq 160$. The contrast is masked by activation overlap of the unimodal conditions as indicated by cyan boundaries. Bar plots at the bottom show mean percent signal change within spheres (5 mm radius) around the peak voxels (across all participants, left: 59 -24 3, right: -57 -33 8) of bilateral superior temporal effects and corresponding *t*-tests. °$P < 0.1$, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, error bars represent 1 SEM. Abbreviations: CVCa = unimodal auditory consonant-vowel-consonant stimuli, CVCv = unimodal visual consonant-vowel-consonant stimuli, SLcon = congruent single letter stimuli, SLinc = incongruent single letter stimuli, CVC-con = congruent consonant-vowel-consonant stimuli, CVCinc = incongruent consonant-vowel-consonant stimuli, all = comparison with all other conditions.


Unimodal auditory CVC
Control
Dyslexic
Control - Dyslexic
Unimodal visual CVC
Control
Dyslexic
Control - Dyslexic
Bimodal congruent CVC
Control
Dyslexic
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μV
t
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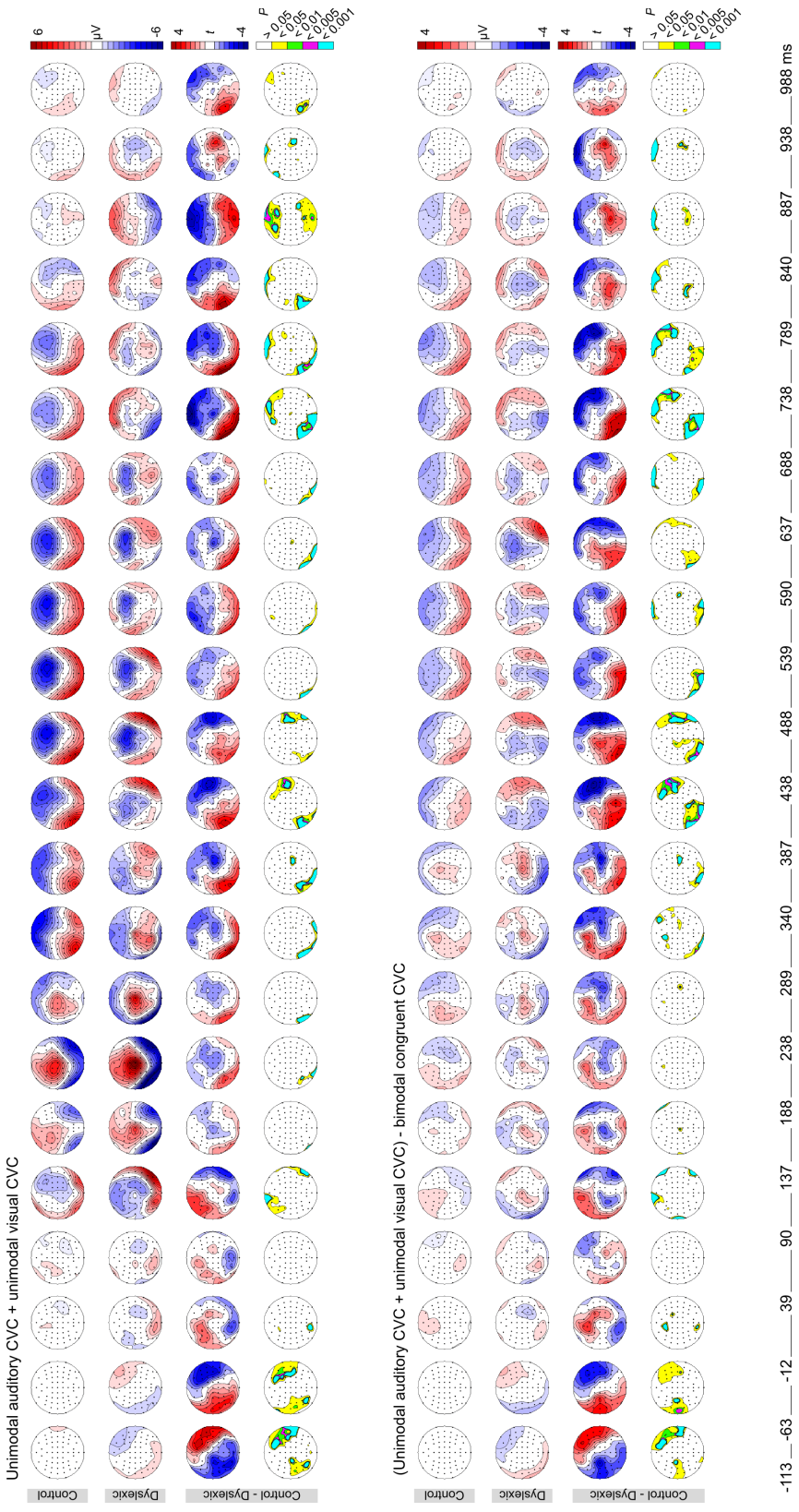

Figure 5.8 Super-additivity: Individual conditions as topographies. Mean voltage map series for the groups separately as well as the groups against one another for the super-additivity contrast and the individual conditions. The first two rows of each panel depict voltage maps for both groups, row 3 and 4 depict statistical *t*- and *P*-maps of the group comparison, respectively. Scales are indicated vertically on the right. Abbreviations: CVC = consonant-vowel-consonant stimuli.

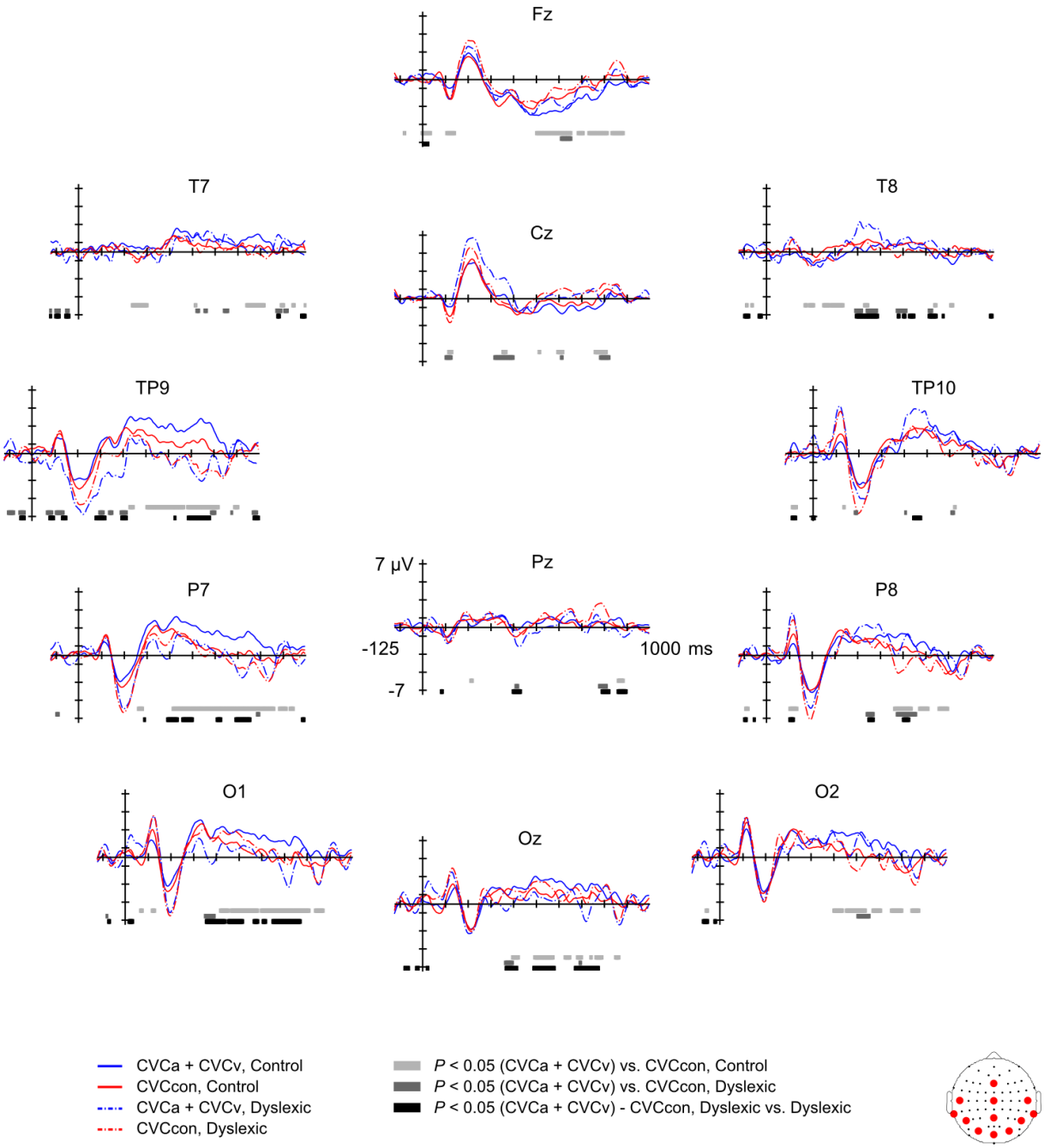

Figure 5.9 Event-related potentials for the super-additivity criterion: summed unimodal and congruent bimodal conditions for both groups. Statistics (running *t*-tests) are not adjusted for multiple comparisons. Abbreviations: CVCa = unimodal auditory consonant-vowel-consonant stimuli, CVCv = unimodal visual consonant-vowel-consonant stimuli, CVCcon = congruent consonant-vowel-consonant stimuli.

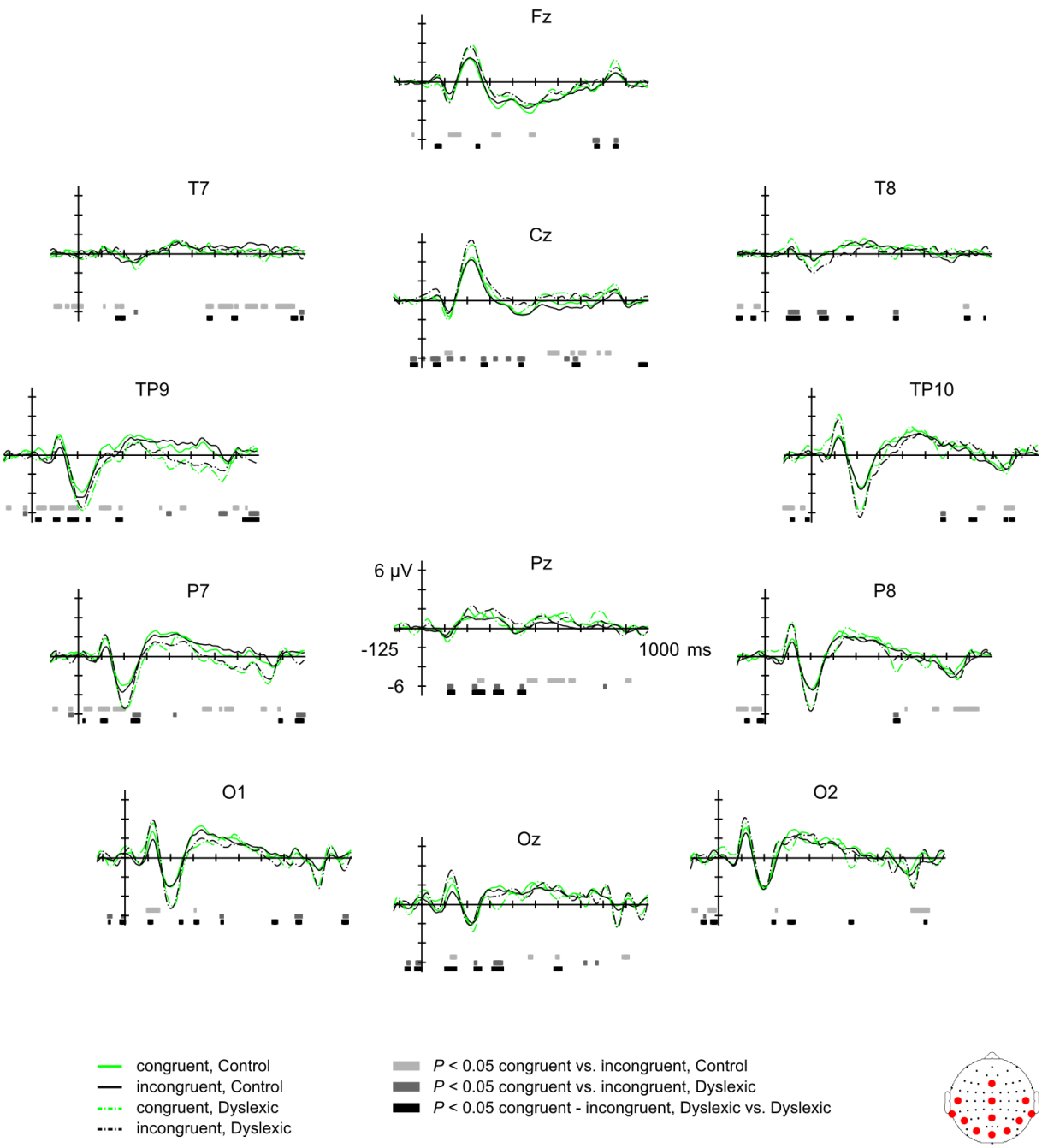

Figure 5.10 Event-related potentials for the congruent and incongruent audiovisual conditions for both groups, pooled across single letters and consonant-vowel-consonant stimuli. Statistics (running *t*-tests) test congruency effects for the groups separately as well as the groups against one another and are not adjusted for multiple comparisons.
Typical readers exhibited early effects (P1, N1) of congruency mode at left occipitotemporal electrodes (O1, P7, TP9), whilst this was not the case in impaired readers. Most consistent group differences were observed during the P1 peaking phase at occipital and temporal electrodes (Oz, O1, P7, TP9), and in the late N1 phase. Most likely, this is also reflected in the TANOVA congruency by group interaction segments that did not pass the duration threshold (Figure 5.3B, p. 72).

5.8.5 Supplementary Tables

Table 5.4 Basic fMRI activation patterns of all conditions. Peak points (MNI coordinates and corresponding brain regions) within significantly activated clusters of each main condition against rest (P < 0.05, FWE) across 35 adolescents (control and dyslexic).

		MNI (x y z)	*Z*-score	Volume (mm³)
CVCa > rest				
Frontal	L Inferior / Middle Frontal / Precentral Gyrus	-36 5 32	6.35	3183
	L Middle Frontal Gyrus	-55 36 24	5.04	54
	L Middle Frontal / Precentral Gyrus	-51 0 47	4.87	41
	R Precentral Gyrus	51 -1 48	5.80	925
	R Inferior Frontal Gyrus (Opercular Part)	36 14 27	5.55	719
Parietal	L Inferior Parietal Lobule	-27 -57 41	5.47	1330
	R Inferior Parietal Lobule	35 -52 44	5.06	145
Temporal	L Superior Temporal Gyrus	-46 -24 9	>8	32866
	R Superior Temporal Gyrus	54 -10 -2	>8	35063
CVCv > rest				
Frontal	L Middle Frontal / Precentral Gyrus	-48 -3 44	6.23	2943
	L Medial Frontal Gyrus	-7 3 54	5.08	128
	R Middle / Superior Frontal Gyrus	53 18 39	6.11	7007
	R Middle Frontal Gyrus	30 53 11	4.89	54
	R Superior Frontal Gyrus (Orbital Part)	26 57 -2	4.84	14
	R Inferior Frontal Gyrus (Orbital Part)	50 44 -12	4.83	7
	R Middle Frontal Gyrus	27 62 9	4.81	17
Parietal	L Superior Parietal Lobule	-34 -61 50	5.93	4080
	R Superior Parietal Lobule	39 -63 53	6.95	8411
Temporal	L Superior Temporal Gyrus	-55 -43 8	5.13	179
	R Superior Temporal Gyrus	50 -37 8	4.84	27
Occipital	L Inferior / Middle Occipital Gyrus	-33 -87 -3	>8	19383
	R Inferior / Middle Occipital Gyrus	29 -88 -2	>8	17429
SLcon > rest				
Frontal	L Precentral / Inferior Frontal Gyrus	-40 -3 38	6.63	8836
	L Medial Frontal Gyrus	-4 3 54	4.84	17
	L Middle Frontal Gyrus	-52 14 44	4.83	10
	R Middle Frontal / Precentral Gyrus	47 -1 47	6.61	7941
	R Medial Frontal Gyrus	0 0 62	4.86	37
Parietal	L Superior Parietal Lobule	-25 -54 45	6.13	4317
	R Inferior Parietal Lobule	27 -57 36	5.80	4755
Temporal	L Superior Temporal Gyrus	-57 -33 12	>8	34864
	R Superior Temporal Gyrus	50 -13 3	>8	34482
Occipital	L Inferior / Middle Occipital Gyrus	-42 -70 -6	7.32	15903
	R Inferior / Middle Occipital Gyrus	38 -79 -3	>8	17543
Midbrain	R Thalamus	11 -30 0	4.87	27
Cerebellum	R Cerebellar Declive	27 -64 -24	4.87	20
Sub-lobar	L Extra-Nuclear / Thalamus	-9 -25 -3	4.86	41
SLinc > rest				
Frontal	L Inferior / Middle Frontal / Precentral Gyrus	-43 5 29	6.76	11566
	L Medial Frontal Gyrus	-6 3 53	5.85	1546
	R Inferior / Middle Frontal / Precentral Gyrus	50 2 47	6.78	5211
Parietal	L Precuneus / Middle Occipital Gyrus	-28 -54 50	6.52	5538
	R Superior Parietal Lobule	35 -57 51	5.11	712
	R Sub-Gyral	30 -54 39	4.78	10
Temporal	L Superior Temporal Gyrus	-49 -37 15	>8	33774
	L Insula	-37 -4 -12	4.87	20

	R	Superior Temporal Gyrus	50 -15 3	>8	48320
Occipital	L	Inferior / Middle Occipital Gyrus	-34 -88 -5	7.25	15586
	R	Middle Occipital Gyrus	32 -64 35	5.19	314
CVCcon > rest					
Frontal	L	Precentral Gyrus	-49 -6 51	5.50	834
	L	Inferior Frontal Gyrus (Opercular Part)	-43 5 29	5.21	368
	R	Middle Frontal / Precentral Gyrus	54 2 47	5.38	564
Temporal	L	Superior Temporal Gyrus	-57 -16 8	>8	28843
	R	Superior Temporal Gyrus	50 -15 3	>8	28029
Occipital	L	Inferior / Middle Occipital Gyrus	-24 -93 -6	7.19	9848
	R	Inferior / Middle Occipital Gyrus	24 -93 -6	7.74	8930
CVCinc > rest					
Frontal	L	Precentral Gyrus	-42 6 27	6.99	10483
	L	Medial Frontal Gyrus	-4 0 56	5.06	182
	L	Medial Frontal Gyrus	-7 12 48	4.90	37
	R	Middle Frontal / Precentral Gyrus	50 -3 47	6.94	2744
	R	Inferior Frontal Gyrus	51 15 27	5.26	1576
Parietal	L	Superior Parietal Lobule	-25 -58 45	5.37	1323
	R	Angular Gyrus / Inferior Parietal Lobule	33 -60 35	5.13	685
	R	Inferior Parietal Lobule	39 -37 29	4.85	10
Temporal	L	Superior Temporal Gyrus	-54 -33 11	>8	39383
	R	Superior Temporal Gyrus	50 -13 5	>8	39032
Occipital	L	Inferior / Middle Occipital / Lingual Gyrus	-31 -87 -3	>8	18549
	R	Inferior / Middle Occipital / Lingual Gyrus	38 -81 -5	7.19	13871

CVCa = unimodal auditory consonant-vowel-consonant stimuli, CVCv = unimodal visual consonant-vowel-consonant stimuli, SLcon = congruent single letter stimuli, SLinc = incongruent single letter stimuli, CVCcon = congruent consonant-vowel-consonant stimuli, CVCinc = incongruent consonant-vowel-consonant stimuli, L = left, R = right

Table 5.5 Sub-additivity, not super-additivity. Peak points (MNI coordinates and corresponding brain regions) within significantly activated clusters of the comparison of congruent CVC stimuli and the sum of unimodal auditory CVCs and unimodal visual CVCs ($P < 0.05$, FWE). There were no super-additive clusters and no group differences ($P < 0.005$, $k \geq 160$).

		MNI (x y z)	*Z*-score	Volume (mm³)
(CVCa + CVCv) > CVCcon				
All participants				
Frontal	L Middle Frontal Gyrus	-54 12 38	4.83	1391
	L Inferior Frontal / Precentral Gyrus	-40 2 35	4.63	773
	L Precentral Gyrus	-52 2 48	4.47	162
	L Inferior Frontal Gyrus (Triangular Part)	-43 14 24	4.16	54
	R Middle Frontal Gyrus	53 15 41	4.60	267
	R Inferior / Middle Frontal Gyrus	53 29 27	4.23	135
	R Inferior Frontal Gyrus (Opercular Part)	36 14 29	4.06	3
Parietal	L Inferior Parietal Lobule	-28 -57 42	4.89	4057
	R Superior Parietal Lobule	36 -60 50	5.31	5508
	R Supramarginal Gyrus	56 -49 38	4.38	176
Temporal	L Inferior / Middle Temporal Gyrus	-54 -46 -12	4.29	101
	L Superior Temporal Gyrus	-64 -51 12	4.09	17
	R Middle Temporal Gyrus	60 -42 -11	4.92	3156
Cerebellum	L Cerebellar Declive	-10 -79 -27	4.33	74
	L Cerebellar Uvula	-33 -66 -32	4.27	84

L = left, R = right, CVCa = auditory only consonant-vowel-consonant stimuli, CVCv = visual only consonant-vowel-consonant stimuli, CVCcon = congruent consonant-vowel-consonant stimuli

Table 5.6 Super-additivity, relaxed criterion. Peak points (MNI coordinates and corresponding brain regions) within significantly activated clusters of the comparison of congruent CVC stimuli and the mean of unimodal auditory CVCs and unimodal visual CVCs ($P < 0.005$, $k \geq 160$). There were no group differences ($P < 0.005$, $k \geq 160$).

	MNI (x y z)	*Z*-score	Volume (mm³)
CVCcon > (CVCa + CVCv)/2			
All participants			
L Superior Temporal Gyrus	-57 -33 8	5.61	3767
R Superior Temporal Gyrus	59 -24 3	6.55	4448
Control			
L Precentral Gyrus	-55 -7 53	4.50	702
L Superior Temporal Gyrus	-60 -31 8	3.95	557
R Superior Temporal Gyrus	60 -27 5	5.29	1988
Dyslexic			
L Superior Temporal Gyrus	-55 -33 8	4.21	2504
R Superior Temporal Gyrus	53 -31 11	4.30	4077

L = left, R = right, CVCcon = congruent consonant-vowel-consonant stimuli, CVCa = auditory only consonant-vowel-consonant stimuli, CVCv = visual only consonant-vowel-consonant stimuli

Table 5.7 Congruency effects tested in ROIs of previous literature. ROI analyses in audiovisual or multisensory integration sites as found in previous studies. The comparison of congruent and incongruent stimuli is shown for both CVC and SL conditions, and the direction and level of significant effects is indicated.

Authors	Date		reported region / ROI	MNI (x y z)	CVCinc <> CVCcon			SLinc <> SLcon		
					All	Control	Dyslexic	All	Control	Dyslexic
Blau et al.	2009	L	STG	-46 -27 5						
Blau et al.	2009	R	STG	45 -23 6						
Blau et al.	2010	L	Planum Temporale	-42 -29 13						
Blau et al.	2010	L	STS	-57 -34 3		> *				
Blau et al.	2010	R	STS	59 -34 1						
Blau et al.	2010	L	anterior STG	-52 -8 1			< *			
Blau et al.	2010	R	anterior STG	58 -9 7		> *	< *			
Hocking et al.	2008	L	posterior STS	-50 -52 8	> °	> **				
Hocking et al.	2008	L	posterior STS	-50 -56 4	> *	> **				
Hocking et al.	2008	R	posterior STS	50 -52 8		> *				
Hocking et al.	2008	R	posterior STS	50 -56 4						
Pekkola et al.	2006	L	STG	-58 -46 14	> °	> *				
van Atteveldt et al.	2004	L	Planum Temporale	-52 -25 10			< *			
van Atteveldt et al.	2004	R	Planum Temporale	53 -17 12						
van Atteveldt et al.	2004	L	STS	-55 -34 6		> *				
van Atteveldt et al.	2004	R	STS	55 -33 11		> °				

ROI = region of interest, CVCinc = incongruent consonant-vowel-consonant stimuli, CVCcon = congruent consonant-vowel-consonant stimuli, SLinc = incongruent single letter stimuli, SLcon = congruent single letter stimuli, All = all participants, > = stronger activation for condition on the left of column heading, < = stronger activation for condition on the right of column heading, °$P < 0.01$, *$P < 0.05$, **$P < 0.01$, STG = superior temporal gyrus, STS = superior temporal sulcus, L = left, R = right.

6 General Discussion

6.1 Conclusion of Study 1 and Contributions to the Field

Study 1 provided clear evidence for reduced print tuning in impaired readers' left vOT cortex. Deficits were observed in a context of minimized phonological or semantic demands, suggesting deficits in print sensitivity at bottom-up processing stages. This finding critically goes beyond previous demonstrations of left vOT underactivation because it proofs that print tuning deficits can be probed independently of phonological processes. This demonstration of stand-alone print tuning deficits is an important contribution to models that postulate incremental left vOT tuning by guidance of phonological reading circuits, i.e., superior temporal brain regions. Study 1 therefore presents unprecedentedly clear evidence that impaired print tuning in adolescent dyslexics might be the long-term consequence of impaired phonological awareness since childhood. If reading skills develop insufficiently, left vOT pathways apparently fail to properly attune to basic elements (e.g., Latin letters) of the respective writing system.

Compared to controls, responses in dyslexia were reduced for all sorts of letter strings but not for false font strings. In the present framework, this finding is interpreted as a coarse rather- than a fine-grained print tuning deficit, given that underactivation was observed irrespective of bigram frequency, pronounceability, or lexicality of the stimuli. The previously reported fine-grained posterior-to-anterior vOT gradient of increasing sensitivity to real words in proficient readers (Vinckier et al., 2007) was not replicated. The reasons for this divergence remain somewhat unclear and more research is needed in order to disentangle the exact functional contributions of regions around the so-called VWFA. The present data suggest bottom-up tuning at the letter level in typical readers and we hypothesize that previous effects of pronounceability or lexicality (Binder, Medler, Desai, Conant, & Liebenthal, 2005; Kronbichler et al., 2007; Kronbichler et al., 2004; Mechelli, Gorno-Tempini, & Price, 2003) had been mediated by phonological or lexical processes that had an impact also on the left vOT cortex. The present interpretation is therefore in line with an interactive account of this brain region (Price & Devlin, 2011), assuming that it serves as an interface for visual feedforward (e.g., orthographic) and top-down phonological (and / or semantic) activations. This account also acknowledges that reading experience results in plastic changes in the left vOT cortex that facilitate recognition of the most commonly occurring orthographic patterns. The present findings indicate that these patterns might be single letters rather than bigrams or whole

words. This possibility has recently been proposed in a meta-analysis (Richlan et al., 2011), but further evidence on bottom-up left vOT tuning is required.

The print tuning deficit in impaired readers was specific to the left hemisphere given that right vOT activation patterns did not differ between groups and did suggest intact functional specialization in dyslexic adolescents. It was also specific to anterior aspects of the left vOT cortex, i.e., the VWFA and anterior (inferotemporal) regions. Hence, deficits were observed in the exact hypothesized region and more general visual deficits in posterior and left occipital brain regions did not account for these specific effects. In addition, robust correlations were observed between reading fluency scores and left anterior vOT regions within the group of typical but not impaired readers. This points to qualitative rather than quantitative differences between the groups and is in line with a lack rather than a lag of systematic print tuning in dyslexia. However, the reliability of such conclusions needs to be treated with caution, considering that group size of the dyslexic sample was rather small and that bottom effects might play a role. Nevertheless, the pattern of correlations corroborates that vOT tuning might represent a proximate marker of reading proficiency or reading impairment as soon as a proficient level has been or should have been reached. The findings therefore also elucidate the unresolved transitions from child- to adulthood in these regions and indicate that a "mature" dysfunction pattern, comparable to the one observed in adults, is already reached in adolescence at the end of compulsory schooling (compare Richlan et al., 2011).

Interestingly, the left STGp showed a gradual activation increase with growing word-likeness in controls. Superior temporal gyri (and sulci) were the target regions of Study 2, given their association with AV integration (e.g., van Atteveldt et al., 2004; Wise et al., 2001). STGp activation also has consistently been linked to phonological decoding and possibly reflects phonological working memory or subvocal articulation (Buchsbaum & D'Esposito, 2008; Demonet et al., 2005; Price, 2000; Wise et al., 2001). The present findings support the role in phonological decoding or, stated differently, grapho-phonological conversion. Activation to words was highest, which suggests highest engagement of grapho-phonological processes, whereas lowest activation for false font strings fits with the absence of grapho-phonological processes. The lack of this gradual response pattern in dyslexics indicates impairments in the automaticity of grapho-phonological engagement, a topic investigated in detail by the second study.

6.2 *Conclusion of Study 2 and Contributions to the Field*

The classical phonological deficit account of dyslexia has increasingly been linked to impairments in grapho-phonological conversion (Blomert, 2011; Brem et al., 2010; Froyen et al., 2011; Harm, McCandliss, & Seidenberg, 2003; Sarkari et al., 2002; Snowling, 1980) and to dysfunctions in superior temporal regions associated with multisensory and AV integration (van Atteveldt et al., 2004; Wise et al., 2001). The aim of Study 2 was to elucidate whether grapho-phonological or AV deficits are more basic and sensory in nature, or whether they are specifically linked to the phonological domain and to phonetic content.

Differences between the response to AV congruent stimulation and the summed unimodal visual and auditory responses served as an indicator of more basic and sensory dimensions of AV integration. Differences in brain responses to phonetically congruent versus phonetically incongruent AV stimulation were taken as an indicator of AV integration at the phonetic level. Integration at the phonetic level was tested for both single letters and three-letter strings. The latter were thought to be more naturalistic and speech-like given that they exhibited rapid phonetic changes that are characteristic for human language and that have been emphasized as a key to a thorough understanding of speech processing impairments in dyslexia (Nagarajan et al., 1999; Renvall & Hari, 2002; Tallal, 1980).

With respect to tests of congruency mode, the results revealed an interesting dissociation across groups in bilateral STG / STS: Whereas responses were stronger for incongruent than congruent stimuli in controls, the opposite pattern was observed in dyslexics. This finding suggested efficient tuning of superior temporal regions to AV congruent stimulation in controls but effortful conversion to incongruent stimuli. In impaired readers, however, effortful grapho-phonological conversion might only be triggered by congruent conditions, whilst incongruent conditions are not processed grapho-phonologically at all. Notably, this dissociation was only observed for the three-letter strings. It is of particular interest for future research that group differences were most pronounced for this condition. So far, multisensory studies have mainly used single letters or phonemes in probing AV deficits in dyslexia (Blau et al., 2010; Froyen et al., 2011; Mittag et al., 2012), which leaves unresolved whether the observed deficits were due to more general and sensory deficits in AV integration, or whether grapho-phonological impairments and the well-documented phonological deficit hypothesis sufficiently account for these findings. With respect to dyslexia, our results provide the first comprehensive comparison of two approaches to testing AV integration (super-additivity and congruency effects) as well as two contexts of testing AV integration at the level of phonetic content (single letters and three-letter strings). They suggested specific impairments at the

phonetic level, that is, in grapho-phonological conversion, especially in a context of speech- and word-like stimulation (three-letter strings). This points to most pronounced impairments when dealing with naturalistic stimulus material. In the endeavour to narrow down the exact functional aberrances around the phonological deficit that affects the majority of impaired readers, further research is certainly needed. The present findings, however, do not imply a sensory or basic deficit in AV integration but rather a specific deficit at the level of phonetic content. This is relieving, considering that basal AV deficiencies should probably cause more severe disruptions than poor reading.

These findings are in line with accounts that conceptualize DD as a deficit to form integrated letter–speech sound objects (Blomert, 2011). They are also in agreement with, although in no direct support of a deficit in the dynamic construction of symbol–sound correspondences that are not necessarily restricted to the domain of familiar speech and print patterns (Widmann et al., 2012). Such a slightly wider perspective would be more suitable to explain deficits in classical phonology tests, such as rapid automatized naming of pictures or digits.

In line with Study 1, less efficient vOT tuning to letter strings in dyslexia was also affirmed by group differences in such regions and in the N1 ERP component.

6.3 Limitations

Before discussing the overall implication of the present findings for the current state of dyslexia research, this paragraph briefly discusses limitations of this thesis.

As discussed in more detail above, the validity of experimental designs exhibited minor limitations for both studies. In Study 1, undesired automatic phonological processes could not entirely be excluded, given their inevitable occurrence in print processing. In Study 2, attentional factors were not fully controlled because it might be possible that controls actively engaged in grapho-phonological matching, whereas dyslexic adolescents were in a more distracted or passive monitoring state. Basically, it was argued that both of these potentially undesired group differences would be the result of the underlying neural deficit rather than the cause for the emergence of differences in brain responses (see the respective sections of each study). However, especially in the domain of AV deficits, future studies should attempt to control attentional factors more precisely, for instance by requiring explicit monitoring of congruency mode or maybe by using priming paradigms that probe subconscious processing. In fact, Study 1 intended to minimize the impact of higher-order attentional factors with its very rapid serial stimulation. In even more rapid or subconscious designs, the question arises whether reading processes are still appropriately probed.

Another point for discussion is the considerable difference in sample sizes. Whereas 22 adolescents could be assigned to the typically reading group, only 13 were classified as dyslexic. This problem emerged because participants were recruited from a pre-defined longitudinal sample and 8 of them that had previously (in 5th grade) been assigned to the dyslexic group did not meet the presently chosen and already quite liberal criteria for dyslexia anymore. However, from a statistical point of view, unequal sample sizes were controlled. Still, correlations in reading scores between 5th and 9th grade were utterly high (words per minute: $R^2 = 0.84$; pseudowords per minute: $R^2 = 0.92$; see Figure 6.1), confirming that relative positions along the scale remain constant (Jacobson, 1999; B. A. Shaywitz et al., 1995; Svensson & Jacobson, 2006). Despite this relative persistence, it would be highly interesting to investigate more closely those participants that showed overproportional improvements. However, this goes beyond the scope of the present thesis.

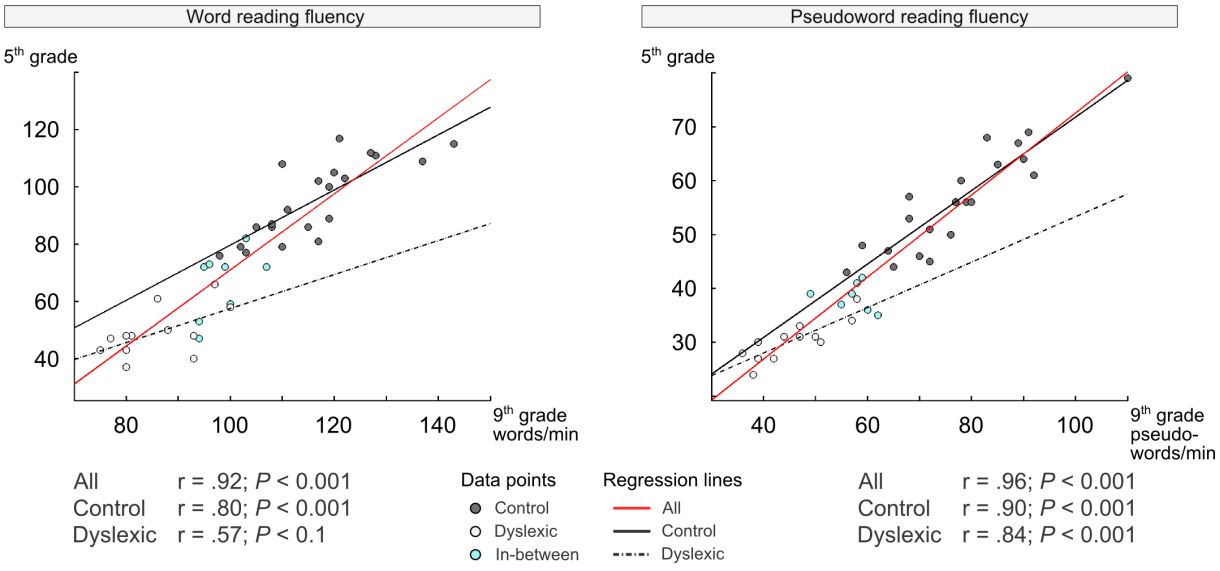

Figure 6.1 Significant correlations between reading fluency measures across time (5th and 9th grade) for the extended sample (N = 43). Reading fluency refers to correctly read items per minute, as shown at the axes. Red, black, and black dotted regression lines are based on the extended sample, the control sample, and the dyslexic sample, respectively. Corresponding correlation coefficients (Pearson's r) and *P*-values are listed underneath each scatter plot.

Another important issue not discussed so far applies to the convergence of fMRI and EEG data. In Study 1, the N1 component of the visual evoked potential indicated print tuning in the left hemisphere of both groups (Figure 4.5, p. 43). Although more robust in controls, this is in contrast to the reliable absence of print tuning in fMRI data of dyslexics. Notably, the origin of the N1 in vOT cortices is among the best-documented ERP source localizations (Allison et

al., 1999; Bentin et al., 1999; Maurer, Brandeis, et al., 2005; Maurer, Brem, et al., 2005; Nobre et al., 1994; Tarkiainen et al., 1999). In other words, signals originating from the same brain region in the exact same context showed different properties in EEG compared to fMRI measures. In Study 2, EEG and fMRI data were convergent with respect to the most prominent effects, that is, main effects of stimulus length (single letter versus three letter stimuli). However, a number of divergent results also casts doubts on the equivalence of both techniques in terms of sensitivity to cortical activation. Many smaller clusters of fMRI congruency effects are not reflected in our ERP analyses. Another example are findings on super-additivity of congruent multisensory stimulation in fMRI data but sub-additivity in EEG data – a finding that is fully consistent with a number of previous publications (see 5.5.1 Super-additivity Effects and Basic Audiovisual Interactions, p. 74) but that has so far not been fathomed.

While some of these divergences can probably be attributed to the low spatial resolution of EEG (and to the low temporal resolution of fMRI), inherent differences in the respective signal properties are probably more appropriate in resolving such harsh contradictions. Electrophysiological recordings, on the one hand, reflect synchronous activity of ensembles of consistently oriented neurons. The detection of activity in closely folded brain structures is therefore impossible due to random or reversed orientations (Michel et al., 2009). The BOLD signal (fMRI), on the other hand, reflects a metabolic correlate of aggregated synaptic activity that is irrespective of cellular orientation (Logothetis et al., 2001; Logothetis & Wandell, 2004). Moreover, both inhibitory and excitatory potentials within a cell ensemble contribute to increases in BOLD signal, whereas this is not necessarily the case in EEG. It is not surprising that particularly the striatal cortex showed convergence in Study 2, given that this region exhibits one of the clearest and homogenous layerings of neurons in the brain and therefore is ideal for electrophysiological signal generation.

In conclusion, the aim to combine two measurement techniques to simultaneously increase spatial and temporal resolution seems promising with respect to very robust and rather extended effects. However, one has to be aware that even these conditions do not guarantee convergence or the desired exploitation of spatial and temporal dimensions. The inherent differences in the signals need to be considered carefully, especially with respect to analyses that combine fMRI and EEG data in the same statistical model, e.g., by using parametric modulation of BOLD activity by EEG measures (e.g., Debener, Ullsperger, Siegel, & Engel, 2006; Eichele, et al., 2005). The latter approach was not employed in this thesis, given that specific questions on DD were the focus rather than the exploration of EEG–fMRI convergence.

7 General Conclusion and Implications for Aetiological Models of Dyslexia

This thesis provides unprecedented evidence for the neural causes of dyslexia at a critical developmental stage, namely at the end of compulsory schooling where reading proficiency is still trained at a high level before literacy experiences diverge due to different professional tracks. Current models on the aetiology of dyslexia are supported by demonstrations of deficits in AV integration at a phonetic level as well as by impaired visual print tuning in bottom-up pathways of the left vOT cortex. Central to both studies were designs intended to delineate more precisely previous ideas of impairments in DD. Study 1 used rapid serial stimulation in order to probe reading-related visual pathways in a bottom-up fashion. Study 2 used several ways of probing AV integration in order to narrow down the recently reported AV deficit hypothesis (Blomert, 2011). Not only do the present findings critically add to current accounts on dyslexia but they are also unprecedented with regard to the participants' developmental stage. Study 1 revealed prominent left vOT underactivation in dyslexic adolescent readers in the context of minimized phonological demands. This is a substantially valid proof of impaired visual print tuning after several years of reading instruction and is interpreted as the long-term consequence of grapho-phonological deficits and as the proximate marker of reading fluency deficits in the matured brain. Study 2 investigated the neural basis of grapho-phonological deficits and critically extended the previous literature by suggesting no deficits in more basic and sensory aspects of AV integration and by showing specific deficits at the phonetic level, especially in a context of naturalistic speech-like stimulation.

The present findings are entirely compatible with the hypothesis of a phonologically guided left vOT tuning to print by perysilvian regions during reading acquisition and a failure of such guidance and tuning in dyslexia (McCandliss & Noble, 2003; Sandak et al., 2004; Schlaggar & McCandliss, 2007; Share, 1995). Impaired guidance by superior temporal brain regions relates to the earliest marker of DD, namely troublesome phonological awareness and processing. It is of little surprise that innate phonological deficiencies also seem to hamper the learning of grapho-phonological conversion rules and the rapid and automatized engagement of such conversions or of phonetic AV integration. Although the exact nature of the innate phonological deficit remains unresolved, the step from the auditory (phoneme) to the visual (grapheme) domain is sufficiently described by such conversions. During normal development, left vOT tuning has been found to follow an inverted-U shape of activation levels with lowest activation prior to learning, highest activation for early stages of reading due to

effortful and inefficient processing, and intermediate activation with expertise and efficient reading (Brem et al., 2010; Maurer et al., 2006; Maurer et al., 2011; Price & Devlin, 2011). The present work indicates that vOT tuning of dyslexic adolescents is lacking and probably stuck in prior-to- or early learning phases. Activation patterns of superior temporal regions were explained by inefficient and effortful grapho-phonological operations in dyslexics. Hence, the two studies support that lacking automaticity of grapho-phonological conversions might prevent a systematic left vOT tuning to print.

This framework is capable of explaining two important characteristics of DD at the behavioural level: The high effectiveness of early phonological training programmes (Brem et al., 2010; Harm et al., 2003; Spironelli et al., 2010) and the high persistence of reading impairments (Jacobson, 1999; B. A. Shaywitz et al., 1995; Svensson & Jacobson, 2006). For children at risk, phonological trainings have the potential to considerably improve starting conditions in mastering grapheme-to-phoneme conversions. This way, the increase in discrepancy between typical and impaired readers during the early years of reading can be alleviated. If such interventions do not occur, the subsequent and severe lack of left vOT specialization remains a persistent cause for reading impairments that can hardly be cured once the brain has matured and the critical phase for reading acquisition has passed. Phonological trainings are cheap and can be conducted at the home computer or in classes. Accompanying aid by speech therapists is advisable.

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10 Curriculum Vitae

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09/1993 – 06/2002	Secondary School: Friedrich-Koenig-Gymnasium, Würzburg, Germany

Occupational Experience

since 08/2013	Data Analyst at Baloise Insurance, Basel, Switzerland Research and development
11/2008 – 06/2009	Internship at Cognitive Brain Research Unit, University of Helsinki, Finland Cognitive neuroscience
05/2007 – 09/2007	Internship at TNS Infratest, Munich, Germany Customer satisfaction research
08/2002 – 05/2003	Community Service (alternative to military service), Würzburg, Germany

11 Publications

Kronschnabel, J., Schmid, R., Maurer, U., & Brandeis, D. (2013). Visual print tuning deficits in dyslexic adolescents under minimized phonological demands. *Neuroimage, 74*, 58-69.

Kronschnabel, J., Brem, S., Maurer, U., & Brandeis, D. (2014). The level of audiovisual print–speech integration deficits in dyslexia. *Neuropsychologia, 62*, 245-261.